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Pharmacological prevention of ischemic stroke and TIA – epidemiological aspects and how to improve treatment

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PHARMACOLOGICAL PREVENTION OF ISCHEMIC STROKE AND TIA – EPIDEMIOLOGICAL ASPECTS AND HOW TO IMPROVE TREATMENT

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For Anna and Alba…

ABSTRACT

Background: Medications can prevent stroke but are not used optimally. The overarching aim of this thesis was to study medication use in patients with previous ischemic stroke or transient ischemic attack (TIA) and in all patients with atrial fibrillation. Socioeconomic and demographic factors such as sex, education, and income have been associated with differences in medication use after stroke. Understanding these associations better may help in understanding reasons for suboptimal medication use. In the chronic setting, patients with a previous stroke are followed in primary care in Sweden. Primary care is thus an important target for improving medication use. All patient visits in primary care require that a diagnosis is recorded by the doctor in the patient's electronic medical record. This "recording" of diagnoses has been hypothesized as a potential quality indicator, but the utility has not yet been proven. Also, the association between diagnosis recording and medication use has not been studied. Audit & feedback is a commonly used approach to achieve changes in behavior in healthcare personnel. Changing the prescribing and motivating behavior of primary care doctors vis-à-vis stroke/TIA and atrial fibrillation patients could potentially increase medication use.

Methods: All the studies in this thesis were registry based and have included patients ≥18 years of age from Region Stockholm. The outcome of all studies has been medication use. By using the Swedish National Prescribed Drug Register (NPDR), we were able to study medication dispensation to patients as a marker of medication use. Study I used cross-linked data from the VAL database (see below), NPDR, and Statistics Sweden. Studies II-IV used data from the local healthcare administrative database for Region Stockholm, the VAL database. Data in VAL is identical to that found in the National Patient Register (NPR) and since 2010 also the NPDR. In study I we explored the association between medication use and socioeconomic and demographic factors 9-12 months after ischemic stroke/TIA. Study II explored the association between diagnosis recording in primary care and medication use for the diagnoses stroke/TIA and acute coronary syndrome. Studies III and IV tested if an audit & feedback intervention in primary care could improve medication use and diagnosis recording in patients with ischemic stroke/TIA (III) or atrial fibrillation (IV).

Results/conclusions: Use of recommended preventive medications in Region Stockholm has increased over time in both patients with prior ischemic stroke/TIA and patients with atrial fibrillation. Although statin use has increased, statins are still the secondary preventive medication class which is used the least after ischemic stroke/TIA. The sex gap in statin use after ischemic stroke/TIA has persisted over time and future interventions should target improving statin use particularly in women. High income was associated with being dispensed more statins, anticoagulants, and antiplatelets 9-12 months after ischemic stroke/TIA. Having a diagnosis recorded in primary care was associated with greater use of antithrombotics and statins in ischemic stroke/TIA, and acute coronary syndrome. Also, recorded atrial fibrillation patients used more anticoagulants. An audit and feedback intervention did not improve the utilization of preventive stroke medications in primary care.

LIST OF SCIENTIFIC STUDIES

The following publications will be referred to in the thesis by their roman numerals.

I. Geary L, Aronius J, Wettermark B, Hasselström J, Sjöborg B, von Euler M.

Sociodemographic factors are associated with utilisation of statins after ischaemic stroke/TIA.

International Journal of Clinical Practice Mar 2017;71.

II. Dahlgren C*, Geary L*, Hasselström J, Rehnberg C, Schenck-Gustafsson K, Wändell P, von Euler M.
*CD and LG contributed equally

Recording a diagnosis of stroke, transient ischaemic attack or myocardial infarction in primary healthcare and the association with dispensation of secondary preventive medication: a registry-based prospective cohort study.

BMJ Open Sep 21 2017;7:e015723.

III. Geary L, Hasselström J, Carlsson AC, Eriksson I, von Euler M.

Secondary prevention after stroke/transient ischemic attack: A randomized audit and feedback trial.

Acta Neurologica Scandinavica Aug 2019;140:107-115.

IV. Geary L, Hasselström J, Carlsson AC, Schenck-Gustafsson K, von Euler M.

An audit & feedback intervention for improved anticoagulant use in patients with atrial fibrillation in primary care.

International Journal of Cardiology Jul 1 2020;310:67-72.

CONTENTS

LIST OF ABBREVIATIONS

ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ARB	Angiotensin II receptor blocker
ATC	Anatomical therapeutic chemical
CDR	Cause of Death Register
CDS	Clinical decision support
CT	Computed tomography
CTTC	Cholesterol treatment trialists' collaboration
ECG	Electrocardiogram
EDI	Equivalized disposable income
EMR	Electronic medical record
ESC	European Society of Cardiology
FDC	Fixed-dose combination
ICD	International classification of diseases
INR	International normalized ratio
ITS	Interrupted time series
LDL	Low density-lipoprotein
MDDD	Multi-drug dose dispensing
MPR	Medication possession ratio
NBHW	National Board of Health and Welfare (Socialstyrelsen)
NOAC	Non-vitamin K antagonist oral anticoagulant
NPDR	National Prescribed Drug Register
NPR	National Patient Register
OR	Odds ratio
PDC	Proportion of days covered
PPV	Positive predictive value
RCT	Randomized controlled trial
SCB	Statistics Sweden (Statistiska centralbyrån)
SMS	Short message service
TIA	Transient ischemic attack

PRELUDE

Taking medications regularly is an important part of preventing cardiovascular disease such as stroke or heart attacks. Life style factors such as smoking cessation, diet, and physical exercise may be just as important as medications. However, life style changes are difficult and medications are not always used optimally. Improving medication use and thereby preventing stroke is the focus of my PhD project. Why do we need to study the subject of medication use? The doctor prescribes you something for your condition and you take the medicine as ordered right? Just pop open the bottle and swallow the tablet with some water - easy! The reality is much more complicated. Taking the appropriate medication in the correct dose, at the correct time, and regularly as intended is a challenge. Why? There are a multitude of reasons. First, the doctor must identify that you need a certain medicine in the first place and then prescribe it. But once the doctor has given you the prescription, taking just one medicine every day seems simple enough right? How easy is it though when you have five medicines to take? Or ten? Moreover, some medicines may need to be taken in the morning, and some in the evening. Patients seldom have symptoms of high cholesterol or high blood pressure, and sometimes atrial fibrillation is asymptomatic. Furthermore, with medicines that treat high blood pressure or high cholesterol or anticoagulants, you don't really see any direct effect. They are taken to prevent something from happening in the future. This can be contrasted against for instance pain medications which give quick relief of symptoms. In this case a patient would be more likely to remember to take them. For patients that have had a stroke or a heart attack one of our most important roles as doctors is to prevent recurrence of disease. Taking medications regularly can reduce a patient's risk of having a new event. This is why medication use interests me greatly and why I feel my project is of great importance.

Because my studies I-IV have many topics, my thesis covers a wide range of subjects. Statins are the secondary preventive medication class which is used the least. Also, in registry studies it is important to know if the diagnoses in the registries are correct, so that you can be certain of studying the correct patients. For these reasons, focus in this thesis will be on statins and the validation of stroke diagnoses in registries.

1 BACKGROUND

1.1 STROKE – EPIDEMIOLOGY AND PREVENTION

1.1.1 Epidemiology of ischemic stroke and TIA

Ischemic stroke and transient ischemic attacks (TIA) cause significant morbidity and mortality in Sweden as well as worldwide[1,2]. According to the Swedish National Stroke Register (RiksStroke) there were 8 430 TIA and 21 090 cases of stroke in 2019, of which 86% were ischemic[2]. The 90-day mortality in stroke patients in RiksStroke was 16% in 2019[2]. Even though symptoms from a TIA by definition resolve spontaneously within 24h, patients are at an increased risk of ischemic stroke the following weeks and months[3].

1.1.2 Socioeconomic- and sex differences in stroke

1.1.2.1 Socioeconomic differences

A low socioeconomic status is associated with worse outcomes in stroke[4]. There are different measures of socioeconomic status, but income and education are two commonly used measures[4]. People with lower socioeconomic status have a higher risk of having a stroke[4]. Furthermore, stroke patients with lower socioeconomic status have higher short term mortality and functional outcome; and have more severe strokes[4].

1.1.2.2 Sex differences

There are also sex differences in stroke. Women are on average 4 years older than men when they have their first stroke[5]. A consequence of this age difference is that women who have a stroke are more likely to be living alone[6], potentially leading to delayed detection and treatment. Also, women may be more likely than men to experience atypical symptoms of stroke, such as generalized weakness or altered mental status[6,7]. On a group level women have different pre-stroke characteristics than men with more atrial fibrillation and hypertension, but less ischemic heart disease[8]. Women have a worse functional outcome than men one year after stroke, and also lower 1-year survival[9]. However, a Swedish study found that when adjusting for multiple confounders, the odds of survival were actually higher in women[9]. Finally, women may be prescribed less secondary preventive medication, particularly statins[2,10].

1.1.3 Prevention of ischemic stroke/TIA

Many aspects of stroke prevention need to be improved[11,12]. Prevention can be divided into primary prevention – preventing the first stroke – and secondary prevention – preventing a recurrence of disease. There are several potential targets for primary prevention in ischemic stroke [13]. Ten modifiable risk factors for ischemic stroke have been identified and may confer up to 90% of the population risk of having a first stroke[13]. The risk factors include diabetes, smoking, hypertension, unhealthy diet, high waist-to-hip ratio, high alcohol use, atrial fibrillation, physical inactivity, and dyslipidemia[13]. Once a stroke has occurred, secondary

prevention becomes important. This includes the prompt identification and treatment of symptomatic carotid stenosis; diagnosing atrial fibrillation; pharmacological treatment; and lifestyle changes[14,15]. The pharmacological component of secondary prevention, i.e. drug treatment, in ischemic stroke/TIA is far from optimal[16].

1.1.3.1 Pharmacological secondary prevention of ischemic stroke/TIA

Pharmacological secondary prevention after ischemic stroke/TIA consists of treatment with several different drug classes, which in most cases are meant to be taken daily and indefinitely[14,15]. Statins are recommended to all patients presumed to have stroke of atherosclerotic origin[14,15]. National Swedish guidelines have for several years recommended that >75% of patients with ischemic stroke should be treated with statins at 12-18 months after their stroke[17]. In 2018 the target levels were increased to >80%[18]. Furthermore, local guidelines in Stockholm have recommended statins for all ischemic stroke/TIA for many years[19], a standpoint which now has support in the litterature[20]. In addition to statins, patients with ischemic stroke/TIA are recommended antiplatelet drugs such as acetylsalicylic acid or clopidogrel. If the patient is diagnosed with atrial fibrillation, oral anticoagulants replace antiplatelets as the drugs of choice. Finally, antihypertensive drugs which lower blood pressure are recommended. European guidelines[14] suggest treating all patients irrespective of blood pressure level whereas American guidelines[15] only recommend treatment if the patient is hypertensive, with a goal of 140/90 mmHg or lower.

1.1.3.2 Atrial fibrillation

Diagnosing and treating atrial fibrillation adequately is an important part of stroke prevention[14,21]. Atrial fibrillation is prevalent in approximately 3% of the Swedish adult population[22] and confers and increased risk of ischemic stroke/TIA[21]. In 2019, 20% of patients with ischemic stroke in Sweden under the age of 80 and 43% over 80 had atrial fibrillation[2]. Atrial fibrillation is slightly more common in men (57% of all patients). This sex difference persists across all age groups[22]. The median age for patients with atrial fibrillation in Sweden is 74, and patients frequently have hypertension, diabetes, and other cardiovascular comorbidity[22,23].

The European Society of Cardiology (ESC) atrial fibrillation guidelines recommend using the CHA_2DS_2VASc scoring system to identify patients with atrial fibrillation at increased risk for ischemic stroke/TIA[21]. The CHA_2DS_2VASc score threshold for treatment with anticoagulants has changed somewhat over the years. The 2010 ESC guidelines recommended anticoagulants in all patients with CHA_2DS_2VASc of ≥ 2 regardless of sex[24]. Since, 2012 treatment with anticoagulants is recommended by the ESC in men with a CHA_2DS_2VASc score of ≥ 2 and women with CHA_2DS_2VASc of ≥ 3[21,25]. According to current ESC guidelines, treatment with anticoagulants can be considered if the CHA_2DS_2VASc score is ≥ 1 in men and ≥ 2 in women[21]. Regardless of how guidelines have changed over the years, a diagnosis of ischemic stroke/TIA concurrently with atrial fibrillation has always been an indication for treatment with anticoagulants[21,24-26].

1.2 THE STUDY OF MEDICATION USE

1.2.1 Clarifying the terminology in medication use research

1.2.1.1 Adherence, compliance, and concordance

Understanding the field of medication use research is complicated by the existence of many similar terms that have often been used interchangeably[27]. The term "*compliance"* has historically been popular in medication use research[27]. Compliance in medication use essentially means the extent to which a patient is taking their prescribed/recommended medication[28]. Compliance may denote a hierarchy in the patient-doctor relationship where the patient's role is to simply follow orders[27,28]. It also suggests that non-compliance is the fault of the patient[28]. The use of the term *"adherence"* has increased in later years[27]. Adherence highlights that the recommended treatment is a result of a patient-doctor interaction and not just a decision on the part of the doctor[28,29]. Thus adherence means the extent to which a patient follows *agreed upon* recommendations/prescriptions[28]. Accordingly, non-adherence is seen as a joint patient-doctor responsibility and does not assign blame only to the patient[28,29]. Concordance, while sometimes being used synonymously with compliance/adherence, does not mean the same thing[28,30]. Concordance is a somewhat complicated term that focuses on patients' views and beliefs and implies a negotiation/discussion process between patient and doctor[28,29,30]. Furthermore, concordance is more difficult to measure than adherence or compliance[30]. A full discussion of the term concordance is beyond the scope of this thesis.

In conclusion, while the terms adherence and compliance are similar, I believe adherence to be the better term since it denotes a more including patient-doctor relationship. Thus I will use term adherence in this thesis.

1.2.1.2 Components of medication adherence

Medication adherence can be divided into three components – initiation, implementation, and discontinuation[27]. *Initiation* is when a patient takes the first dose of a prescribed medication[27]. *Discontinuation* is immediately after the patient has taken the last dose[27]. *Implementation* is the time period between *initiation* and *discontinuation*[27]. The *implementation* is the time period where it can be determined to what degree the patient follows the agreed upon dosing plan as intended[27]. Questions that can be answered by studying the implementation period include – Are the correct number of doses taken each day? At the correct time? Are doses missed? Furthermore, primary non-adherence denotes a patient not picking up the first prescription of the medication[10].

1.2.1.3 Persistence

Persistence means the time period from initiation to discontinuation[27]. If a patient is persistent to treatment it means that they continue to take the prescribed medication, having initiated treatment at some point. If patients are asked if they are still taking a medicine twelve months after starting treatment and they answer "yes" then they may be considered persistent. However, we have no idea how adherent they are. They could potentially only

have picked up two 90-day prescriptions during the twelve months in which case they would only have had pills lasting for half of the 12 months. In this particular situation patients are considered to be persistent to treatment, but they are most definitely non-adherent.

1.2.2 Why is the study of medication use important?

Persistence to recommended mediations declines with time after ischemic stroke leading to potentially worse outcomes for patients[16]. The positive effects of good adherence/persistence to preventive medications on the prevention of cardiovascular disease have been reported in several publications[31-37].

1.2.3 How can medication use be studied?

Medication use can be studied using many different methods, all of which have advantages and disadvantages[38]. Methods can be *subjective* or *objective*, with the most common subjective being self-reported medication use or doctor-reported use[38]. Furthermore, methods can also be divided into *direct* or *indirect*[38]. Direct methods study the drug content in bodily fluids, like blood or urine, and are objective. Indirect methods can be both subjective and objective. The subjective, indirect methods include patient interviews, questionnaires, and scales, like the commonly used Morisky Medication Adherence Scale[38]. Finally, the objective, indirect methods include pill counting; using electronic medication packaging devices; and registry/database analysis. A discussion of the strengths and limitations of all the above methods is beyond the scope of this thesis. I will focus on the registry/database methodology since this is what was used in all the studies in this thesis.

1.2.4 Why did we choose to use registries/databases in our studies?

Registries/databases are being used increasingly to study medication use[39,40]. Using registries/databases in medication use research has many advantages. It does not inconvenience patients. Also, it has the advantage of being cheap, and enabling the study of medication use in large populations over longer periods of time[39]. Using any of the other of the direct or indirect measures in a large population of patients would be enormously resource consuming, and often unfeasible.

1.2.5 An important limitation – dispensation ≠ taking a medication

Often, registries contain dispensation data[41]. As can be seen in figure 1, taking a prescription medication entails several steps, one of which is picking up the medication from the pharmacy – being dispensed. However, being dispensed a medication does not mean that a patient takes it in the intended way, or at all. Furthermore, if a registry only contains information on dispensation and not prescription, which can be the case[41], the mechanisms underlying non-adherence/non-persistence can be difficult to ascertain. If a patient has not been dispensed a medication it can either be because they have not picked up an existing prescription or that the drug has not been prescribed by the doctor.

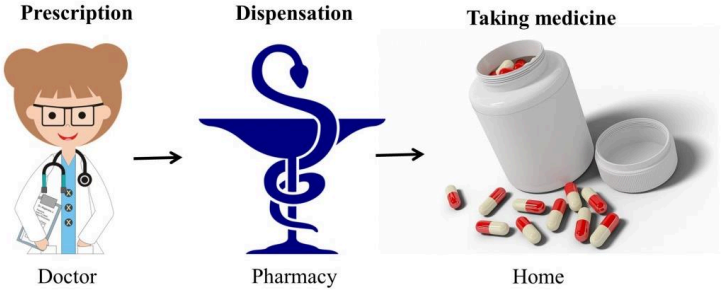


Figure 1. An illustration of the chain involved in patients taking their medication. Images downloaded from www.pixabay.com and are free to use commercially.

1.2.6 Methods for studying medication use in registries/databases

There are an abundance of specific methods for studying medication use in registries/databases[38]. This section will give a short introduction to some of the more commonly used methods, and methods used in the studies in this thesis.

1.2.6.1 Medication Possession Ratio and Proportion of Days Covered

Registry dispensation data can be used to approximate *adherence* by calculating the Medication Possession Ratio (MPR) or the Proportion of Days Covered (PDC). These are two of the most commonly used methods in adherence research[33]. They are similar but with some small differences[42]. The MPR summarizes all the daily doses dispensed in a defined time period and divides that number of daily doses with the number of days in the time period. This has the obvious disadvantage of sometimes overestimating adherence if a patient choses to pick up dispensations early. In these cases the MPR can be >100%, which can make population studies challenging if the researcher is studying an average of the MPR. The PDC can never exceed 100%. When calculating the PDC, the number of days that are covered by dispensed medication in the study period are also calculated. However, since the maximum number of days which can be covered in a study period of 60 days is 60 days, the maximum PDC is 100%.

1.2.6.2 Persistence

Persistence can also be studied in registries. Often, a patient is considered to be persistent to treatment if they continuously pick up the medication during a period. In this type of study in registries there is generally a "grace period" which is the time allowed from the time one dispensation runs out until the next prescription is filled[16]. Imagine a situation where a prescription lasting 100 days is picked up on day 0, and the researchers employ a grace period of 30 days. Providing the patient takes a daily dose, the prescription will have run out on day 100. To be considered to be persistent to treatment the patient needs to pick up a new prescription before day 131. If studying persistence after two years, the calculation continues for all prescriptions during that period, or until the patient is defined as non-persistent by not having picked up medication in the appropriate interval (30 days).

1.2.6.3 Number of dispensations in a time period

This is the method used in the studies in this thesis. One way to study medication use in registries/databases is by measuring if a patient picks up a medication a certain number of times during a time period of interest[43,44]. An example can be picking up two dispensations in a year in Sweden, where each dispensation generally lasts approximately three months. This method can be used to reflect medication use in the chronic setting and shows that a patient is taking the medicine and likely intends to continue to take it.

1.3 THE REGISTRIES/DATABASES USED IN OUR STUDIES

1.3.1 Cross-linking of registry data in Sweden

Registry data in Sweden can be linked to other registries thanks to the personal identification number which is given to all people who live in Sweden on a permanent basis[45]. The actual linkage is done at the National Board of Health and Welfare (NBHW, Socialstyrelsen). In our study I, data from Statistics Sweden was cross-linked to other registry data.

1.3.2 The National Patient Register

The Swedish National Patient Register (NPR) records all patient discharge diagnoses in hospitals[46]. It was started in 1964 and has since the start been improved in several ways, including identifying patients using the Swedish personal identification number and including patient diagnoses from specialized outpatient care[46].

1.3.3 The National Prescribed Drug Register

The Swedish National Prescribed Drug Register (NPDR) started in July 2005[41,47]. It contains medication dispensation data on all prescribed medications which have been dispensed in the entire country[41,47]. Examples of included data in the NPDR are the anatomical therapeutic chemical (ATC) code of the dispensed medication, the brand name, strength, package size, date of prescription, prescribed amount, and date of dispensation.

1.3.3.1 A special situation in the NPDR - Multi-dose drug dispensing

Sweden has a system of multi-drug dose dispensing (MDDD) where patients are dispensed ready packed doses of medicine according to their medication list, in sealed plastic bags (known commonly as "Apodos")[48]. Patients with MDDD often live in nursing homes[49]. Deliveries generally occur every two weeks and every delivery is counted as one dispensation in the NPDR[50]. It should be noted that dispensations in MDDD do not require any active action on the patient's part. Using a specified number of dispensations in a time period to define being on-treatment in studies, may not accurately approximate real medication use in this group of patients. Sometimes they patients with MDDD are excluded from studies on medication use[51].

1.3.4 Statistics Sweden

Data on socioeconomy and demography is kept by the government agency Statistics Sweden (SCB), which is responsible for national official statistics in Sweden[52]. Data on income, highest level of achieved education, and country of birth can be extracted and linked to other registries.

1.3.5 The VAL database

The VAL database is the local healthcare administrative database for Stockholm County (From 1st January 2019 renamed Region Stockholm) and has been in use since the 1980s[53]. It actually consists of several databases but for the purposes of simplification they will be referred to as one database in this thesis[54]. VAL was created to plan, follow up and evaluate quality and economics of health care financed by the region[53]. A large number of variables related to healthcare use are recorded in it[53,54]. Hospital discharge diagnoses are recorded in VAL, and are sent by Region Stockholm to the NPR[53]. Thus, discharge diagnoses are identical in VAL and the NPR. Furthermore, primary care diagnoses are registered in VAL, data which is not available on a national level[53]. Also, since 2010, VAL contains data on medication dispensation, which is reported to VAL from the Swedish eHealth Agency[54]. The Swedish eHealth Agency also supplies data for the NPDR[47]. Thus, dispensation data in VAL and the NPDR are identical. However, in study I dispensation data had to be acquired from the NPDR since it was not available in VAL at the time[54].

1.4 MEDICATION USE AFTER ISCHEMIC STROKE/TIA

1.4.1 Initiation of medication and chronic management

Ischemic stroke, TIA, and atrial fibrillation are conditions for which chronic treatment with medication is warranted and this chronic treatment is generally managed by primary care doctors in Sweden. As stroke patients are generally treated in hospital when they have their event, medication therapy is initiated in hospital in most cases. In Sweden, prescriptions are valid for one year from the date they are issued[55]. Thus, after one year, patients need new prescriptions. Follow up routines in Sweden differ somewhat regarding ischemic stroke and TIA, but generally patients are not followed up by the hospital after one year. The responsibility then falls on primary care. In atrial fibrillation, treatment with anticoagulants may be initiated either in hospital or in primary care, but prescriptions in the long term are generally handled in primary care. The one exception in Stockholm has been with the advent of non-vitamin K antagonist oral anticoagulant (NOAC) treatment where NOAC treatment initially was handled by hospitals and specialist outpatient clinics[56].

1.4.2 Medication use after ischemic stroke/TIA is suboptimal

1.4.2.1 Overall interpretation of the literature

When going through the literature from more than five years ago (when my PhD project was started) it is clear that medication use after ischemic stroke/TIA was suboptimal for all

medication classes but better for anti-hypertensives and anti-platelets than for statins and anticoagulants. I believe that the most representative data on medication use after ischemic stroke/TIA comes from registry/database studies on large, unselected populations using dispensation data[10,16,57].

1.4.2.2 Studies on persistence and the limitations of studying only persistence

Persistence to medical therapy after ischemic stroke/TIA is 56-76% for statins[10,16,34,58,59], 74-95% for antihypertensives[10,16,58-60], 45-96% for antiplatelets[10,16,31,58-63], and 32-90% for anticoagulants (in patients with atrial fibrillation)[10,16,58-62,64]. These studies have only included patients who had received a prescription for, or were taking the medication in question, on discharge. Thus, simply data on medication persistence cannot be used to appreciate the proportion of all patients with previous ischemic stroke/TIA who are treated with the medication in question. For example, in a Swedish registry study of 21 077 ischemic stroke patients, only 7 275 patients were discharged with a statin prescription[16]. At two years the number of persistent users was 3 556 which gave a persistence of 56%. Another study observed a statin persistence of 76% at one year after ischemic stroke/TIA[58]. Only 1 830 out of 2 457 (78%) patients received a prescription at discharge.

1.4.2.3 Cross-sectional studies evaluating medication use

Other studies evaluating cross sectional medication use in patients with prior ischemic stroke/TIA, irrespective of prescription status, have found that 40-57% use statins[57,65], 74-86% antihypertensives[57,65], 74-100% use antiplatelets[57,65-67], and 13-76% use anticoagulants[57,65,67,68] (in patients with atrial fibrillation). The study observing 13% use of anticoagulants was from in China[67], whereas the other two studies observing 54%, 63%, and 76% were from Sweden[57], the Czech Republic[65], and Germany[68].

1.4.2.4 Study heterogeneity and limitations

Studies on medication use after ischemic stroke/TIA exhibit methodological, geographical and temporal heterogeneity. When performing a systematic literature search, I identified 16 relevant studies, which relate to medication use after ischemic stroke and TIA. Some studies were excluded due to low quality and/or inadequate description of the methodology. Methodological limitations were present in many of the 16 studies, particularly those reporting high persistence. There were four *single center studies*[34,60,63,64], and these are less likely to be generalizable to other contexts since there may be unique characteristics in that specific center that are not applicable to other settings. *Loss of follow up* was an issue in two studies. There was loss of follow up of around 10% in one study[59]. In the other study, centers with <80% data collection were excluded, which led to an exclusion or loss of follow up of 66% of patients originally eligible for analysis[62]. There were only five out of 16 studies which *used dispensation data* to define persistence or medication use[10,16,31,57,63]. All the other non-registry studies used self-reported medication use at a certain time point after the

ischemic stroke/TIA. Self-reporting will likely give a higher persistence than the dispensation based approach with grace periods, which is a more strict definition. Also, *registry/database studies have the advantage of including large, unselected cohorts* of patients with prior ischemic stroke/TIA. This will limit selection bias which may be present in other studies which apply inclusion/exclusion criteria, and experience loss of follow up. There were only three studies matching that description, all from Sweden[10,16,57]. Registry/database studies also have the advantage of patients not being affected by them being included in a study. The study that observed the highest persistence to antihypertensives (95%) was also a single center study and patients were contacted at six and twelve months, which may have affected their medication use[60]. One study reporting persistence of 89% to antiplatelet therapy and 79% to anticoagulants, was in the context of a clinical trial and may not reflect the real life situation[61]. In the study reporting the highest anticoagulant persistence (90%) only 70% of patients with atrial fibrillation and stroke were discharged with an anticoagulant[64]. Some studies may not be generalizable because they are conducted in a very specific context, like one Chinese and one Spanish study which selected patients in neurological outpatient clinics[66,67]. Interestingly, the Spanish study is the only one of the 16 identified studies that used a direct method for evaluating medication use – 66 patients who received aspirin all exhibited thromboxane A_2 synthesis inhibition, indicating that all patients were taking aspirin[66].

1.5 ANTICOAGULANT USE IN ATRIAL FIBRILLATION IS SUBOPTIMAL

Medication use in atrial fibrillation has historically been suboptimal, both in Sweden and internationally[22,23,69,70]. There are sex and age differences in treatment with women and the elderly using less anticoagulants[22,23,70-73]. The mechanisms underlying sex differences in anticoagulant treatment in atrial fibrillation are not clear. Suggested contributing factors have been the possible increased risk of bleeding in women taking warfarin[71,74,75]. Another contributing factor may be the increased prevalence of complicating comorbidities in women[23], and that women with atrial fibrillation in general are older than men[22].

In addition to patients with a clear indication not being treated with anticoagulants, inappropriate treatment has also been a problem. In 2011 in Stockholm, 30% of men and 32% of women with CHA_2DS_2VASc score 2-4 were only treated with aspirin[23]. For CHA_2DS_2VASc score 5-9 the proportions were 36% for men and 40% for women[23]. Conversely in low risk patients, 24% of men with CHA_2DS_2VASc 0 used anticoagulants, and 18% of women with CHA_2DS_2VASc 1[23].

1.6 MECHANISMS OF SUBOPTIMAL MEDICATION USE

1.6.1 General mechanisms

Patient non-adherence is multifactorial and complex. Osterberg reviews potential predictors of non-adherence in general in an article from 2005[76]. Among potential predictors of non-adherence in general are psychological problems, asymptomatic disease, inadequate follow-up, side-effects, lack of belief in benefit, lack of insight into illness, and complexity of

treatment[76]. Physicians are likely implicated in some of these predictors through failure to explain benefit or side effects of medications[76]. Adherence can be classified as unintentional – i.e. forgetting – or intentional – i.e. motivational problems, not understanding benefits of medications or other beliefs concerning medications[77]. Data on reasons for suboptimal medication use can be acquired in different ways. Sources can be qualitative interview studies, questionnaire studies or registry/database studies. Information from qualitative interviews has the advantage of giving more detailed reasons for non-adherence whereas registry/database studies often only provide an association.

1.6.2 Mechanisms in stroke patients

When studying the literature on non-adherence in stroke from qualitative or questionnaire studies many of the reasons for non-adherence seem to be intentional. *Concerns about medication* is a recurring theme[78-83]. These concerns about medication may partially be a fear of side-effects. This is worrying since many stroke patients do not know, or understand, the possible side-effects of medications after hospital discharge[84]. A second theme revolves around the *understanding* of different aspects of treatment such as why medications are supposed to be taken, potential benefits, and the chronic nature of the disease [58,78,83,85-87]. If patients are not sure of the benefits of a medicine, it stands to reason that they are more likely to discontinue it if they have side-effects. Also, if they do not understand that they have a chronic disease which needs life-long treatment, they are probably more likely to stop their treatment. Patients in a study set in a low socioeconomic setting in the US stated low trust in their doctor and problems communicating with their doctor as reasons for non-adherence [82]. Patients with a previous stroke often have cognitive symptoms which could theoretically lead to forgetting/unintentional non-adherence. However, a meta-analysis on non-adherence to medications after stroke found no association with cognitive impairment[88]. A possible explanation is increased support from care-giver and/or home nursing [89].

Studies reporting associations between different factors and higher or lower medication use after stroke are very heterogeneous and thus hard to draw any conclusions from[16,31,34,51,58-61,90-92].

1.7 IMPROVING MEDICATION USE AFTER STROKE

1.7.1 Feasible interventions that can improve medication use after stroke in large populations are lacking

One purpose of this thesis was to find ways of improving medication use in a large population of patients with previous ischemic stroke/TIA in Region Stockholm. Two systematic reviews of interventions aimed at improving the use of medications after stroke have not, identified any studies which can be used to improve medication use in large populations of stroke patients[93,94]. The few interventions that may be beneficial have limitations, and require considerable resources, which make them hard to introduce on a broad scale. Furthermore, few studies have focused on improving long term medication use in the primary care setting[93,94].

1.7.2 Studies with beneficial effects and their limitations

1.7.2.1 Study characteristics

Two systematic reviews have included studies evaluating interventions that could improve medication use after stroke[93,94]. One included interventions focusing on medication use specifically and identified 17 studies[93]. The other included interventions aimed at improving control of modifiable risk factors after stroke (42 studies), of which medication use was an outcome in 21 of the studies[94]. Only nine out of 38 studies in the two reviews found any beneficial effects on medication use[93,94]. There were many different components of the interventions, which varied between studies[93]. Interventions included educating and motivating patients; simplifying medication regimes; home visits; regular telephone follow up; and addressing patient concerns and beliefs[93,94].

1.7.2.2 Limitations of the studies showing benefit

Although nine of the 38 studies found beneficial effects on medication use, there were significant limitations[95-103]. Three of the nine studies did not include a control group[96,97,100], and another did not adequately randomize[95]. Five studies had relatively short follow up of three months[98], six months[103] and one year[97,101,102], respectively. Although not necessarily a limitation, only three of the nine studies were in a community setting[95,96,100], and the others were initiated in hospital[97-99,101-103]. Overall, the number of included patients was small with seven of nine studies including 20-414 patients[95-99,101,103]. In the study with 20 patients, most patients were adherent to begin with[96]. Most of the interventions were resource consuming[95-97,99,101,102]. For example, in one hospital based study the intervention included contacting patients by telephone at 2, 6, 12, and 52 weeks; involvement of primary care physicians; 24 hour ambulatory blood pressure monitoring; mail send outs with personalized risk factor profiles; educational sessions; and in-person follow up[97].

1.8 IMPROVING MEDICATION USE IN ATRIAL FIBRILLATION

Few interventions have been able to increase the use of anticoagulants in the primary care setting. However, a multinational study of approximately 2 000 patients showed that a complex educational intervention targeting both doctors and patients increased use of anticoagulants[104]. The increase in proportion of patients using anticoagulants was 68% to 80% in the intervention group, and 64% to 67% in the control group. Aside from this one publication, which was somewhat resource consuming, results from other studies have not been convincing[105-110]. The main focus of these other studies has been some form of decision support tool for doctors.

1.9 AUDIT & FEEDBACK FOR IMPROVING MEDICATION USE

Audit & feedback was the method used in the intervention in studies III and IV. This section will give an introduction to audit & feedback; the rationale for choosing it as the intervention; and an overview of previous intervention studies involving audit & feedback.

1.9.1.1 Audit & feedback – what is it?

Audit & feedback is an extensively studied method for changing healthcare provider behavior. A Cochrane Collaboration analysis of the effectiveness of audit & feedback from 2012 included 140 clinical trials, of which 49 had audit and feedback as their sole intervention[111]. In the other 91 trials, audit and feedback was a major component of a more complex intervention. "Audit and feedback" consists of a summary of clinical performance ("audit") which is then provided ("feedback") to the doctor/provider in question. In general "audit and feedback" shows positive results for dichotomous outcomes with a median adjusted difference of 4.3 % absolute increase[111]. The results can however be both negative, with a 9% decrease of desired behaviour, and positive, with a 70% increase[111].

1.9.1.2 Why did we choose audit & feedback as our intervention?

As mentioned in section 1.7.1, few interventions have previously targeted improving medication use in large populations of stroke patients in the primary care setting. Since audit & feedback has the potential for affecting the medication taking behaviour of a large number of patients through a proxy (their doctor), we felt that it was a suitable methodology for our purposes. Audit & feedback may be a way to change physician behaviour in the area of prescribing and thus increase medication use in patients. Physicians choosing not to prescribe medication[16], or patients discontinuing medication on physician advice[58], may be important factors in suboptimal medication use in stroke. The process of patients taking their medication entails several steps (figure 1). Physicians have an important influence on all steps. They prescribe medications and then motivate patients to pick them up, take them, and be adherent to therapy. Thus, achieving physician behavioural change can potentially have a positive effect on all the steps in patient medication use.

1.9.1.3 Audit & feedback research in primary care

Audit & feedback is widely studied in primary care with 60% of the studies (84/140) in the Cochrane meta-analysis being in that setting[111]. Studies using audit & feedback alone or as a part of a larger intervention in primary care have targeted a wide variety of areas. Examples include, but are not limited to, number of radiographs requested according to guidelines[112]; management of hypertension[113-116]; number of lab tests ordered[117]; cancer [118]; blood pressure screening[119]; lipid screening/testing[119,120]; mammography[121] or smoking cessation referrals[122]; compliance with diabetes guidelines[123]; time in therapeutic range for international normalized ratio (INR)[124]; osteoporosis management[125]; and identification/diagnosis of dementia[126].

1.9.1.4 Audit & feedback prescription research in primary care

In addition to the above described areas of research, prescription is a widely targeted area for audit and feedback interventions in primary care[115,127-137]. Both a decrease and an increase in prescribing behavior could be targeted in the studies, with the decrease often concerning antibiotics or benzodiazepines.

1.9.1.5 Audit & feedback in coronary heart disease in primary care

Some studies of audit & feedback have targeted the management of coronary heart disease in primary care, most with neutral results[138-145]. The studies are heterogeneous with regard to size, type of complex intervention combined with audit and feedback, and end-points that were targeted. Two studies showed positive results on prescribing of antiplatelets[141,145], one of which also studied statins[145], also with a positive outcome. These studies were however small, randomizing 28 primary care centers[141] and 28 primary care physicians[145], respectively.

1.9.1.6 Audit & feedback in stroke in primary care

No studies of audit & feedback have, to our knowledge, specifically targeted improving prescribing or medication use in stroke prevention in primary care. One study has targeted improving antiplatelet drug prescription in TIA patients[146]. Audit and feedback has been used in different stroke studies, but it has often been from a hospital perspective[147-152].

1.9.1.7 Audit & feedback in atrial fibrillation

I performed a literature search on audit & feedback and atrial fibrillation and only identified four studies[146,153-155]. One study is yet to publish results[155], and two were in a hospital setting and did not include a control group[153-154]. The fourth study had controls and was in a primary care setting[146]. In this fourth study, audit & feedback was a component of a more complex intervention. The intervention did however not show any convincing results on the use of antithrombotics in atrial fibrillation patients.

1.10 RECORDING A DIAGNOSIS FOR GREATER LONG TERM MEDICATION USE?

1.10.1.1 Recording a diagnosis – definition and hypothesis

Our definition of recording a diagnosis is that patients receive the same or a related diagnosis in primary care as they have received upon hospital discharge for a certain condition (study II). We hypothesized that recording of a diagnosis would be associated with greater long-term medication use in both stroke/TIA, and ischemic heart disease patients.

1.10.1.2 Rationale for studying diagnosis recording

Our hypothesis was that recording a diagnosis could be a quality indicator for adequate care of patients with chronic conditions and may be important in overall quality improvement. There is a great interest in developing quality indicators for improving the quality of care, Sweden already uses quality indicators to compare care between regions and the United Kingdom has used primary care quality indicators for many years[156-158].

In 2016, the organization Sweden's Municipalities and Regions (Sveriges Kommuner och Regioner), launched a service called Quality in Primary Care ("PrimärvårdsKvalitet")[159]. This service is a national system for quality indicators with automatic data extraction from

parameters registered in the electronic medical record (EMR). In 2020, 80% of primary care centers in Sweden had access to quality indicator data on their patients. Important to note is that "Quality in Primary Care" is based on diagnoses recorded in each primary care center. Thus, each center will only attain quality data from patients with diagnoses, but not those without. This raises an important point of why diagnosis recording may be important. A first step in quality improvement of specific chronic diseases, such as ischemic stroke/TIA, is to identify the prevalence of the condition. Thereafter an audit of different outcomes of quality is possible. In Sweden, regulation limits the use of diagnoses recorded outside of the own care giver. Thus, if a large proportion of patients with certain conditions remain unrecorded, primary care centers cannot know the true prevalence of chronic conditions in their own center. Consequently, quality improvement becomes more difficult.

Why not study long-term patient medication use directly through dispensation data in the NPDR as a quality indicator, instead of diagnosis recording? Medication use data is likely a useful quality indicator. Our notion was however that recorded patients using more preventive medication could be a surrogate marker for better overall care of the condition in question. There are many aspects of chronic stroke care which require the attention of the physician. These include, but are not limited to, identifying and treating secondary conditions such as incontinence, shoulder pain, central post-stroke pain, depression, and osteoporosis[160]. Other important aspects of chronic stroke care are fall prevention; assessment of cognition and memory; and assessment of swallowing[160]. However, many of these conditions and assessments are however difficult to measure compared to medication use. Thus, we wanted to perform an initial proof of concept study to see if diagnosis recording could be associated with patient outcomes. In study II this patient outcome was the use of recommended secondary preventive medication in patients with previous stroke/TIA or acute coronary syndrome. In study III and IV we tested if an audit & feedback intervention could improve diagnosis recording.

1.11 SETTING

In all the studies we have selected the patients from Region Stockholm. It is an urban region of approximately 2.4 million people[161]. There are six hospitals in the region with emergency departments (a seventh, Karolinska University Hospital Solna only admits patients with referrals) and approximately 200 primary care centers.

2 AIMS

The overall aim of the PhD-project was to study medication use in patients with previous ischemic stroke/TIA and in patients with atrial fibrillation. Aims of specific studies were:

Study I: To identify socioeconomic and demographic factors associated with medication utilization 9-12 months after ischemic stroke/TIA.

Study II: To study if having a diagnosis recorded in primary care was associated with using more secondary preventive medication after stroke/TIA and acute coronary syndrome.

Study III and IV: To study if an audit & feedback intervention (appendix figure A1) in primary care could improve preventive medication use and diagnosis recording in patients with previous ischemic stroke/TIA (III) and atrial fibrillation (IV).

3 METHODOLOGICAL CONSIDERATIONS

3.1 STUDY DESIGN AND DATA SOURCES

	Study design	Registries/databases	Number of patients
Study I	Retrospective cross-sectional	VAL, Statistics Sweden (SCB), NPDR	19 335
Study II	Prospective cohort	VAL	19 072
Study III	Block randomised controlled trial	VAL	12 766
Study IV	Block randomised controlled trial	VAL	31 477

Table 1. Study design, registries/databases used, and number of patients included in studies I-IV. NPDR=National prescribed drug register. The VAL database is the local healthcare administrative database for Region Stockholm.

3.2 TIME PERIOD OF THE STUDIES

The time periods from which patient cohorts were selected for the studies in this thesis is shown in figure 2. Study I included ischemic stroke/TIA patients from the 1st January 2006 to the 31st of August 2010. Study II included patients with ischemic or hemorrhagic stroke, TIA, or acute coronary syndrome (ACS) from the 1st of January 2010 to the 31st of December 2013. For study III and IV we used two different cohorts of patients with ischemic stroke/TIA and/or atrial fibrillation diagnoses. The first cohort included patients from the 1st of July 2009 to the 30th of June 2014 (index period A), and the second patients from the 1st of January 2011 to the 31st of December 2015 (index period B).

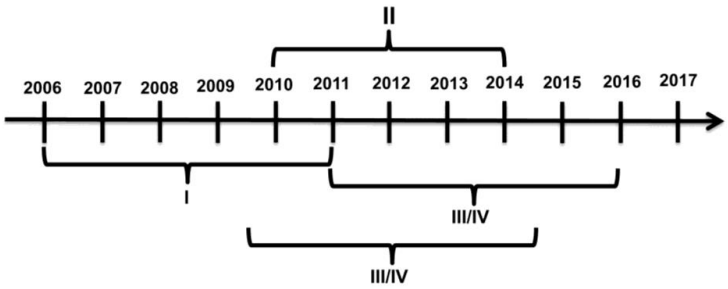


Figure 2. Time periods from which patients in the cohorts in the studies in this thesis were included.

3.3 OUR MAIN OUTCOME - MEDICATION USE

3.3.1 Outcomes in studies I-IV

We defined medication use as a certain number of dispensations in a defined time period. We chose one dispensation in a 4 month period in study I, two dispensations in a one year period in study II and two dispensations in an 18 month period in study III and IV.

3.3.2 We wanted to study all patients, not only those with prescriptions

Why did we choose to study a certain number of dispensations during a time period instead of studying adherence or persistence? The main reason for choosing this definition of medication use was that we wanted to study *all* patients (with certain exclusion criteria) with previous ischemic stroke/TIA in study III and all patients with atrial fibrillation (with CHA_2DS_2-VASc ≥2) in study IV. As has previously been mentioned in this thesis, the study of adherence and persistence (with the exception of primary adherence) generally means studying patients who have initiated treatment[27,38]. We wanted to study all patients in study II-IV since they all had indications for treatment according to local guidelines in Stockholm[19]. The rationale for choosing two, rather than one, dispensations during a time period in study II-IV was that it may better reflect an intention to continue treatment than just one dispensation. It should be noted that, even if all patients have an indication for treatment, the goal cannot be to treat 100% of patients after ischemic stroke/TIA with all recommended medications. Some patients will develop intolerable side-effects, or may have contraindications.

To summarize, medication use in this thesis describes how medications are dispensed in an entire cohort of patients with a certain prior diagnosis, and not just those who have received prescriptions.

3.3.2.1 Terminological considerations in study II

In study II we used the phrase "Data on dispensation of medications in the entire patient cohort was extracted as a **marker of adherence**". In retrospect, I believe that it may have been better to simply write "as a marker of patients **using the medication** in question". Good adherence is generally seen as a PDC or MPR ≥80%[33]. In our patients in study II, two dispensations (most often 100 pills per dispensation) in 12 months that was the definition of being treated (or adherent), would have covered 55% of days (200/365) in most cases. Thus, it is not entirely appropriate to use the term "adherence". Conversely, it should be noted that the term "good medication use" is a broad term which can be used to describe both good adherence and/or good persistence.

3.3.2.2 A special situation – warfarin

The study of medication use for warfarin is more complicated than for other medication classes, if the intention is to study adherence or persistence. For statins, antiplatelets, and antihypertensives, the daily dose is often one tablet of each separate medication. In warfarin treatment, patients require different doses, and thus a different number of daily tablets to achieve the desired INR, often 2.0-3.0[162].

The required daily dose of warfarin for a specific patient, at a specific point in time, is not available in the NPDR in Sweden. Thus it is difficult to approximate the number of warfarin dispensations which a patient needs during a year. Warfarin in Sweden is available in 100 tablets per dispensation. Doses required can vary greatly from patient to patient, with a mean

of 4.2 mg/day required[162]. One tablet is 2.5 mg. Thus 100 tablets in one dispensation can be estimated to last for approximately 60 days, for a mean daily required dose. It follows that a patient taking warfarin will require more than one dispensation in a year. Thus, a patient with atrial fibrillation who picks up at least two warfarin dispensations in a specified time period in the chronic treatment context, similarly to other medication classes, likely has the intention of continuing treatment. This was the basis for our definition of using medication as multiple dispensations in a time period.

3.4 STUDY DESIGN CONSIDERATIONS AND LIMITATIONS

3.4.1 Socioeconomy, demography, and statin use (study I)

The aim of study I was to evaluate the impact of socioeconomic and demographic factors on the long term use of statins after ischemic stroke/TIA. For this purpose, we selected the time period 9-12 months after ischemic stroke/TIA as our dispensation interval.

3.4.1.1 Choice of time interval

In retrospect the time interval 9-12 months is somewhat arbitrary. The rationale was that by selecting a time period of one year after the initial event, we would capture the long term use of statins, when primary care has assumed the prescribing responsibility. The main flaw in the choice of the time period 9-12 months is that patients may still have prescriptions available from their hospital physician at this point in time as prescriptions can last for, and cover, one year. For short term use it may have been more appropriate to study the dispensation of a statin in the first three months after discharge and for long term use, a time period after one year. For example, medication use could have been defined as two dispensations in the time period 12-24 months after ischemic stroke/TIA.

3.4.1.2 Including prescription data from RiksStroke and more data from the NPDR

One option could have been to include prescription data at discharge as a variable, by linking data to RiksStroke. Also, we could have included more data on dispensations from the NPDR, rather than just dispensations in the 9-12 month period after the event. Then we could have obtained information on several outcomes - primary non-adherence, adherence, persistence, and medication use in all patients - and their association with socioeconomic and demographic factors. Such a study design could have yielded further relevant information, not available from the results in study I.

3.4.2 Diagnosis recording and medication use (study II)

The aim of study II was to investigate the association between diagnosis recording in primary care and medication use in stroke, TIA, and ACS.

3.4.2.1 ICD-code selection for index and recording period

In all my studies, the patients have been included on the basis of having, or having had, a disease. Thus, to be sure that the correct patients have been included in the study, selecting

the appropriate international classification of diseases (ICD) codes is of vital importance. Ischemic stroke will be used as an example. In the index period in study II, we wanted to be sure, with a high level of certainty, that our stroke patients had actually had an ischemic stroke. Thus, we limited the number of ICD codes which qualified the patient as having had an ischemic stroke. Thus, we selected patients with ICD codes I63.0-9 (see supplementary material for study II for all ICD codes). All I63.0-9 ICD codes start with "cerebral infarction" and then continue with for example "due to embolism" or "due to thrombosis" and whether or not the affected vessel is pre-cerebral or cerebral[163].

In contrast, for the recording period we wanted to have a high degree of sensitivity, i.e. we wanted to capture all diagnoses which may have pertained to a previous ischemic stroke. The purpose was to ensure that we captured as many ischemic stroke patients as possible who received a diagnosis in primary care which could be assumed to be related to their ischemic event. This meant that we accepted ICD codes such as I64.9 "Acute cerebrovascular disease not specified as hemorrhage or infarction". The rationale for being permissive with diagnosis selection in primary care is that the patterns of diagnosis selection are very variable. Not all primary care doctors routinely choose a cerebrovascular disease diagnosis at their patient's yearly check-up. They may simply choose another of the patient's diagnoses such as hypertension or type-two diabetes.

3.4.2.2 Duration of the recording period

In study II, we selected patients with a stroke/TIA or ACS diagnosis in a one year period and then followed them for a further three years (figure 3). The exposure was if patients received a primary care diagnosis equivalent to their initial hospital diagnosis in years two and three after their event (recording period, figure 3). We chose a two year interval for the recording period to allow for patients who were followed in primary care, but not annually, to be recorded.

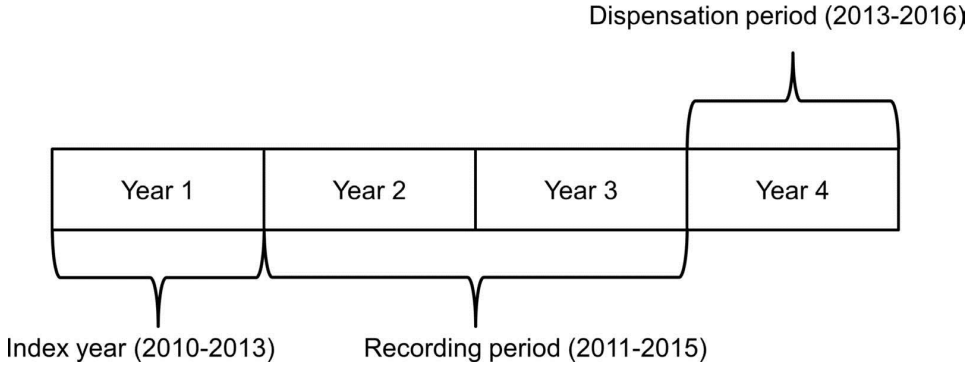


Figure 3. **Definitions of index, recording, and dispensation period in study II.** From Dahlgren C, Geary L, Hasselstrom J, et al. Recording a diagnosis of stroke, transient ischaemic attack or myocardial infarction in primary healthcare and the association with dispensation of secondary preventive medication: a registry-based prospective cohort study. BMJ open 2017;7:e015723.

3.4.3 Audit and feedback interventions (study III and IV)

The aim of study III was to evaluate the effect of an audit and feedback intervention in primary care on medication use and diagnosis recording in patients with previous ischemic stroke or TIA (study III) and atrial fibrillation (study IV).

3.4.3.1 Block randomization

Primary care in Stockholm is organized into nine areas of continuous medical education, within which most educational initiatives are based. The rationale for not randomizing all approximately 200 primary care centers to either intervention or control was that there may be a spill-over effect of the intervention between centers in the same educational area. Thus, we felt it more prudent to randomize all centers within an entire area of continuous medical education to either intervention or control.

3.4.3.2 Norrtälje centers were excluded

One area of continuous medical education in Region Stockholm is Norrtälje. We excluded primary care centers in Norrtälje, since the organization of healthcare there is different than in the rest of the region, with a uniquely integrated model of healthcare and services[164,165]. A publicly owned, privately run company (Tiohundra AB), organizes and runs both the local hospital, the primary care centers, and the municipality-run health care services[164,165]. The integrated model means that the mechanisms behind diagnosis recording would have been completely different to the rest of the Region, since patients in Norrtälje receive both acute and chronic treatment for their stroke/TIA within the same organization.

3.4.3.3 Who to target with the intervention – doctors directly or center directors?

We sent the quality reports (intervention) to the primary care center directors in the intervention centers. An alternative could have been to send the reports personally to individual doctors in all intervention centers. We wanted to use an existing framework where the hope was that the directors would use and disseminate the reports internally, using them for quality improvement, internal education etc. Our concern was that doctors in primary care receive a wide variety of educational material and that our intervention would have become simply “another information pamphlet”.

3.4.3.4 The components of the intervention

The center directors received the quality reports (see figure A1 in appendix for de-identified version), but also a PDF-file with PowerPoint slides which clarified the data in the reports. Additionally, the slides contained information on national goals from the National Board of Health and Welfare and one slide with a “call to action” regarding stroke prevention. This slide contained questions such as “do we know which of our patients have had a stroke?”; “are we following up our stroke/TIA patients annually?”; “are we identifying patients with atrial fibrillation?”; “what are our patients’ characteristics in our RAVE-reports?”; “can we improve our routines?”. Furthermore, an information letter was included, in both the e-mail,

and the regular mail. In this letter, directors were encouraged to arrange an internal meeting and present the information. Finally, we included a letter, briefly describing how the quality reports could be used as the mandatory quality improvement project for the region.

3.4.3.5 Diagnosis recording was defined differently in study II and study III/IV

We used a different model to define diagnosis recording in study III and IV compared to study II. Instead of an index year (figure 3), we used a diagnosis from the index period and then evaluated if patients received a primary care diagnosis during the 18 month dispensation period (which was also the recording period in study III/IV). The main differences between definitions of diagnosis recording in study II and III/IV are illustrated in figure 4.

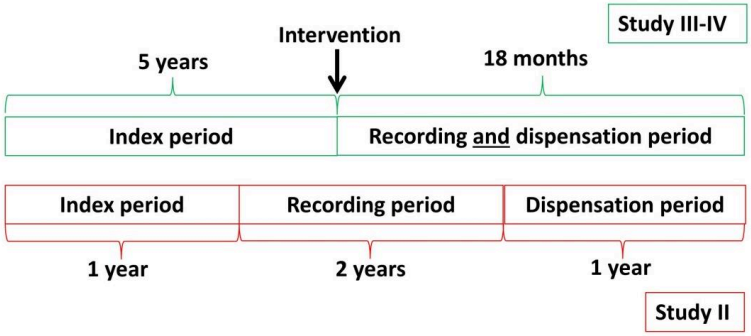


Figure 4. **Different definitions of periods used for defining diagnosis recording in studies II and III/IV**. Diagnosis recording was defined as having an initial diagnosis during the index period and then being diagnosis recorded in primary care in the subsequent recording period.

In addition to differences in the definitions of index and recording periods between studies II and III/IV, the models used for studying diagnosis recording were different in other respects. Patients with multiple diagnoses were not excluded in studies III and IV since we wanted to include all patients in the control and intervention centers to reflect the real life situation of follow-up. In study II we wanted to be sure that patients were followed in primary care for the condition in question as it was a proof of concept study for the association between diagnosis recording and medication use. Had we included patients with more hospitalizations for a specific condition, we would not have been sure if the hospital or the primary care center were responsible for care. Furthermore, if we had included patients with hospital visits for several conditions, we could not have been certain of which treatment guidelines applied to the patient in question.

Furthermore, our original data set for study III/IV did not cover a long enough time period to allow for the same analysis model as in study II. To determine if the intervention had any effect on diagnosis recording using the model from study II, a time period of two years would have to elapse to allow for the two year recording period to occur after the intervention (figure 5). Our original data set only covered the time period until June 2017. It is possible to

use the model from study II in the future but it will require an amendment of our data set and we currently do not have funding for this.

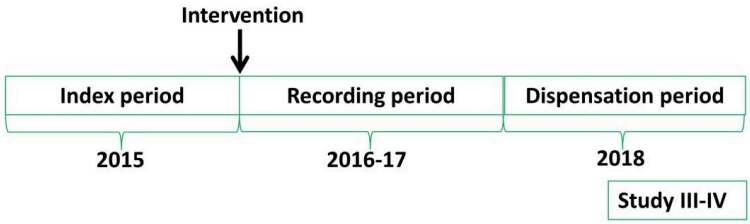


Figure 5. **Description of how diagnosis recording could have been analyzed in study III and IV according to the model from study II.** Our original data set only covered the time period until June 2017 and thus the model in this figure could not be used.

3.4.3.6 Which CHA_2DS_2VASc score when analyzing data in study IV?

We chose to analyze all patients with $CHA_2DS_2VASc \geq 2$, in study IV in accordance with local treatment guidelines at the time of the study, which were also included in the intervention[19]. In March 2017 local Stockholm guidelines were updated to match ESC recommendations[166]. We performed sensitivity analysis in study IV (unpublished), defining a clear treatment indication as CHA_2DS_2VASc score of ≥ 2 for men and CHA_2DS_2VASc of ≥ 3 for women in accordance with the ESC recommendation at the time of the study[25]. We wanted to analyze only patients with a clear indication for treatment, which was the rationale for not including all atrial fibrillation patients in the analysis of the intervention.

3.5 COMPARING MEDICATION USE IN STUDY I AND III

We used different methods to study medication use in study I and III, which should be considered when interpreting the data. Study I defined medication use as one dispensation in the period 9-12 months after ischemic stroke/TIA and study III as two dispensations in an 18 month period following a five year index period. While the dispensation period in study I was exactly 9-12 months after discharge for all patients, the time period between event and dispensation period varied greatly in study III. Since the index period in study III was 2011-2015, a patient included in study III could for example have had their event on the 1st of January 2011 or on the 31st of December 2015. Since the dispensation period was the 1st of January 2016 to the 30th of June 2017, this means that patients in study III could have the start of their 18-month dispensation period anywhere from one day to five years after their event. Finally, in study III we excluded patients living in nursing homes; patients not registered at a primary care center; and patients in the excluded primary care centers. These exclusion criteria were not applied in study I.

3.6 VALIDITY OF THE REGISTRIES USED

All studies in this thesis have used registries/databases. The patient cohorts in the studies were included from registries/databases and the outcomes have also been extracted from registries/databases. Thus, it is important to know validity of the registries/databases used.

3.6.1 Validity of the NPR vs validity of VAL for stroke diagnoses

Stroke diagnoses in the VAL database have, to my knowledge, not been specifically validated. However, since the data on discharge diagnoses are identical in VAL and the NPR[53], validity studies on stroke diagnoses in the NPR should be applicable to VAL. The only caveat being that the NPR is based on national data, whereas the VAL only contains data from Region Stockholm. Thus, differences in validity cannot be ruled out, but are likely small.

3.6.2 What does validity mean?

For a diagnostic test, the tests validity is its ability to measure what you intend it to measure. To know if the NPR is valid with regards to stroke diagnoses two questions need to be answered – 1) are all patients with stroke captured in the NPR registry? and 2) does a stroke diagnosis in the NPR mean that the patient has actually had a stroke? These questions can be answered by studying the *sensitivity* and the *positive predictive value* (PPV) for stroke diagnoses in the NPR.

3.6.3 What is the gold standard for stroke incidence in a population?

To be able to answer the questions posed above (1 and 2), a prerequisite is that we have some way of identifying all patients with stroke in a population, a gold standard. The gold standard for determining the true number of strokes in a population entails searching for strokes in both hospital populations, primary care populations, and cause of death registries[167].

3.6.4 How is sensitivity calculated?

Sensitivity answers question (1) above – what proportion of strokes are captured in the registry? Sensitivity can be calculated as seen in figure 6. Imagine that the gold standard has identified 800 “true” strokes (“Stroke (+)”) in a population. 600 of these patients receive a discharge diagnosis of stroke in the NPR, 200 do not. Then the sensitivity, i.e. the number of positives in the NPR relative to true number/gold standard, is 600/800=0.75=75%.

	Stroke (+)	No-stroke (-)
Stroke in NPR (+)	600	
No Stroke in NPR (-)	200	
Total	800	
Sensitivity	600/800=75%	

Figure 6. Illustration of how the sensitivity of a registry can be calculated relative to a gold standard reference ("Stroke (+)"). NPR = national patient register. The sensitivity in the above example is 75%.

3.6.5 How is the positive predictive value calculated?

In addition to the sensitivity of a registry, the positive predictive value is also of interest. While the sensitivity can tell us the proportion of patients with true diagnoses that are missed in our registry (25% in the example in figure 6), the PPV answers question (2) – what is the likelihood of a registry recorded stroke diagnosis actually being true? Imagine a situation where the NPR has diagnosed 700 patients with stroke in a population (figure 7). The gold standard tells us that 100 of those patients actually did not have a stroke ("Stroke (-)") and were miss-classified in the NPR. Thus, the PPV is 600/700=0.86=86%.

	Stroke (+)	No-stroke (-)	Total	PPV
Stroke in NPR (+)	600	100	700	600/700=86%
No Stroke in NPR (-)	200			
Total	800			
Sensitivity	600/800=75%			

Figure 7. Illustration of how the positive predictive value (PPV) of a registry can be calculated relative to a gold standard reference. NPR = national patient register. The PPV for a stroke diagnosis in the NPR in the above example is 86%.

3.6.6 Swedish studies of stroke incidence

Several Swedish studies have attempted to ascertain all cases of stroke (both ischemic and hemorrhagic) within a specified community[168-170] using hospital, primary care, and cause of death data. Two of them have only attempted to find all first time events of stroke[168,169] with one focusing on all strokes[170]. The "gold standard" community data from these studies has been used to evaluate the sensitivity and the PPV of the NPR[168-171] (one of the studies[169] did not specifically intend to evaluate validity against the NPR, but data can still be used for this purpose).

3.6.7 Sensitivity of the NPR for stroke diagnoses

The sensitivity of the NPR for detecting all strokes is high, 83-94%[170,171], with the reference gold standard of true strokes being ascertained thorough community studies of stroke incidence. The study which reported 83% sensitivity included patients found in the Causes of Death Register (CDR) in the denominator[171]. If these patients are excluded, then the sensitivity of the NPR is 90% rather than 83%. Three studies report the sensitivity of the NPR for a first ever stroke to be 84-86%, but these studies have also included dead patients in the denominator[168,169,171]. If the dead patients were to be excluded, sensitivity would be higher. Furthermore, in one of the studies, 8% of patients with stroke were evaluated in the emergency department and then sent home for outpatient management[169]. Had they been admitted, as may be the practice in other settings, sensitivity would have been 92%.

3.6.7.1 Why is the sensitivity of the NPR not 100%?

As described above the sensitivity of the NPR is not 100% for finding all strokes/TIAs that actually occur in a defined community population. Most, but not all patients in Sweden are treated in-hospital for ischemic stroke/TIA[168-170]. Patients not treated in hospital for stroke will likely be missing from the NPR, which contains hospital discharge diagnoses and specialist outpatient clinic diagnoses. Some patients die from their stroke before being admitted to hospital. These cases are not found in the NPR, but can sometimes be identified in the CDR[169,170]. Some patients treated in hospital for stroke may not receive a stroke diagnosis at discharge[168]. This is a relatively uncommon occurrence and may be more likely in patients treated outside of stroke wards[168].

3.6.8 Positive predictive value of a stroke diagnosis in the NPR

PPV answers question (2) in the earlier section – is the stroke diagnosis in the registry correct? While an older study from 1992 reported a PPV of 69% for a stroke diagnosis in the NPR[170], more recent studies have described much higher PPVs, 88% for all stroke[171] and 94-97% for a first stroke[168,171]. The study reporting a PPV of 69% was carried out in 1985-1988, when radiological methods for detecting stroke and identifying potential differential diagnoses were not as widely available. This may partly explain the higher PPV in more recent studies.

3.6.8.1 Why is the PPV of the NPR not 100%?

Why are some stroke diagnoses in the NPR wrong? Patients diagnosed with stroke in the NPR may have had other diagnoses than stroke such as epilepsy or an anoxic brain injury[168]; received a stroke diagnosis despite diffuse symptoms (vertigo, confusion) and the absence of focal neurological deficit[170]; may have received an incorrect acute stroke diagnosis despite only having sequelae after a previous stroke[170,172]; have been miss-classified as TIA[170]; and finally may have had a traumatic brain injury and not a stroke[172].

3.6.9 Other sources of validation – RiksStroke

The national quality registry for stroke, the Swedish Stroke Register, "RiksStroke"[173,174], can be used to estimate the PPV of stroke diagnoses in the NPR. This can be done since RiksStroke annually registers the completeness of data with regards to stroke and TIA diagnoses[172]. A lot of effort is put towards only including patients with actual stroke in RiksStroke. Designated staff in stroke units check for the appropriateness of patient inclusion. This means that a stroke diagnosis in RiksStroke is very likely to be a true stroke diagnosis. To put it another way - the PPV of a stroke diagnosis is likely to be higher in RiksStroke than in the NPR. Participation in RiksStroke is voluntary, but non-participation is extremely rare.

3.6.9.1 Completeness of stroke diagnoses in RiksStroke

RiksStroke is compared annually to the NPR with regards to completeness. This means dividing the number of patients in RiksStroke with a first ever stroke by the total number of patients in the NPR with a first ever stroke diagnosis. The rationale for selecting the first ever diagnosis when evaluating completeness is that differentiating recurrent stroke vs stroke sequelae can be difficult. The completeness has been high, around 90%, for many years[172,175].

3.6.9.2 Relating the completeness of RiksStroke data to the validity of the NPR

A stroke diagnosis in RiksStroke has a high PPV, i.e. is likely to be a true stroke. Thus, the fact that around 90% of first time stroke diagnoses in the NPR are also found in RiksStroke, means that the PPV of a stroke diagnosis in the NPR is also likely to be high.

3.6.10 Validity of ischemic stroke and TIA diagnoses specifically in the NPR

3.6.10.1 Ischemic stroke

Studies on the validity of the NPR have focused on stroke diagnoses, not further specified[168-171]. Thus, all types of stroke are included in these studies, both ischemic and hemorrhagic. Given that the large proportion of stroke, around 85%[2], is ischemic, validity studies on all stroke should be, in large part, applicable to ischemic stroke as well. Personal communication with the RiksStroke representatives has also revealed that unpublished data supports the high PPV of ischemic stroke diagnoses in the RiksStroke registry.

3.6.10.2 TIA

The validity of TIA diagnoses in the NPR has, to my knowledge, not been studied. The TIA diagnoses in the RiksStroke registry have however been validated. A sample of 180 TIA patients were extracted and the patient journals were reviewed by two assessors, one neurologist and one physician with a specialist interest in neurology[176]. In 93% of cases, at least one of the assessors found a TIA diagnosis to be likely or possible. In 77% of cases both assessors agreed that a TIA diagnosis was likely or possible. The completeness (also compared to the NPR) of a first time TIA diagnosis in RiksStroke is 85%, but has only been recorded since 2018[172].

TIA is a more difficult diagnosis than stroke in the sense that sometimes a diagnosis is recorded based solely on patient history, with no objective findings on physical exam or radiology. This fact, together with the completeness being 85%[172] and the aforementioned validation study[176], gives to reason that the PPV of a TIA diagnosis in the NPR is lower than for stroke, but may still be relatively high.

3.6.11 Validity of the NPR regarding atrial fibrillation diagnoses

While the PPV of an atrial fibrillation diagnosis in the NPR is likely high, with one study reporting 81%[177] and another 97%[178], the sensitivity is probably lower[177]. In the second study, 97% was the combined PPV for the NPR and the CDR[178]. The reference gold standard in the studies was electrocardiogram (ECG) documented atrial fibrillation[177,178]. The first study, which reported both PPV (81%) and sensitivity of atrial fibrillation diagnoses, included 336 patients with ischemic stroke, and 336 age- and sex matched controls without stroke[177]. In total the sensitivity of an atrial fibrillation in the NPR was around 80% in this cohort of 672 patients[177]. For stroke patients (n=336), sensitivity was 82%, and 76% for the control group (n=336)[177]. Thus around 20% of atrial fibrillation diagnoses may be missed if only using the NPR as a source. The VAL database has the advantage of also containing primary care diagnoses. Since some patients may be managed in primary care and only receive their atrial fibrillation diagnosis there, combining the NPR, with hospital diagnoses, and primary care data (as in study III and IV) will give a higher sensitivity than the NPR alone[179].

3.6.12 Definition of the CHA_2DS_2VASc score

Diagnoses from both the NPR and primary care (from VAL) were used to create the CHA_2DS_2VASc variable in study IV. We have used somewhat different definitions of the variables included in the CHA_2DS_2VASc score than some other authors[23,44]. This will lead to a lower prevalence of some of the CHA_2DS_2VASc variables in our atrial fibrillation cohort in study IV compared to some other studies[23,44]. However, the different definitions of the variables in the CHA_2DS_2VASc score will likely have affected intervention and control centers similarly thanks to randomization, and thus will not have affected the neutral results of the intervention.

3.6.12.1 Lower prevalence of vascular disease

The validity of myocardial infarction diagnoses in the NPR is high[46]. However, in our study, our definition of the "vascular disease" variable in CHA_2DS_2VASc has led to us reporting a lower prevalence of vascular disease than some other studies[23,44]. The vascular disease variable in our CHA_2DS_2VASc score was defined as any previous ACS or peripheral vascular disease diagnosis during a five year period. We may have found more patients if we had selected a longer time period, e.g. ten years. Also, we only included unstable angina pectoris (ICD I20.0), but not the other chronic forms of angina. Furthermore, the I70 diagnosis code (different versions of peripheral atherosclerosis) was not included in our definition of peripheral vascular disease. Taken together, these definitions led to 9% of the

patients our cohort of atrial fibrillation patients 2011-2015 having vascular disease (unpublished results). These 9% of patients have a high likelihood of having true vascular disease. However, when comparing to contemporary publications, it is obvious that we have not included all patients with true vascular disease. These contemporary publications from Region Stockholm reported a vascular disease prevalence of 24% and 25%, respectively[23,44].

3.6.12.2 Lower prevalence of diabetes and ischemic stroke/TIA

We used the dispensation of any antidiabetic medication during a 5 year period to define the presence of diabetes mellitus. This will likely capture patients with clinically relevant diabetes mellitus, but will give a marginally lower prevalence than when diabetes diagnoses are used to define the presence of disease[23,44]. The high validity of stroke diagnoses in the NPR has been previously discussed in this thesis. There are two reasons for the lower prevalence in our study compared to other studies[23,44]. We only included ischemic stroke and TIA diagnoses from the NPR, and used the ICD codes I63; G45.0-1; G45.3; and G45.8-9. This is a more strict ICD-code definition of ischemic stroke/TIA than other studies, which often include more unspecific diagnoses such as I64 and I69.4, and diagnoses from primary care[23,44]. Also, we did not include diagnosis codes for systemic embolization.

3.6.12.3 Heart failure

Two studies validating heart failure diagnoses in the NPR have shown a relatively high PPV [180,181], meaning that patients with a heart failure diagnosis likely have heart failure. Both studies used ESC guidelines as the gold standard[180,181]. A thorough review of medical records and collection of relevant information including, but not limited to, echocardiography, x-ray, and ECG results was performed in both studies[180,181]. A PPV of 82% was reported in a study from 2005[180]. In patients where an echocardiography was performed, PPV was 88%[180]. However, while the PPV was 95% for a primary diagnosis of heart failure, the PPV dropped considerably if the diagnosis was in position 3-6 (63%)[180]. This study has the obvious draw-back of including only men[180]. A more recent Swedish study included a random sample (n=965) of all patients discharged or deceased with a heart failure diagnosis from 2000 to 2012 in a large hospital in the west of Sweden[181]. In this sample, 62% of heart failure diagnoses were classified as definite, and 32% as probable. When only studying patients with a heart failure diagnosis 2009-2012, the proportion of definite cases increased to 83%[181]. Thus, in that region, the PPV of heart failure diagnoses in the NPR has increased with time.

Like some other authors[23,44], we defined heart failure as having a diagnosis in the NPR or primary care (from VAL). Thus, we have likely captured more heart failure diagnoses than if we had only used the NPR. The prevalence of a heart failure diagnosis in patients with an atrial fibrillation diagnosis in 2011-15 was 28% in study IV (unpublished results), which is slightly lower than some similar studies[23,44]. These small differences are likely explained by different exclusion criteria and that we did not include right heart failure in our definition (I50.0).

3.6.12.4 Hypertension

Our study had the advantage of including primary care diagnoses for the variable hypertension. This is relevant since a large proportion of hypertension diagnoses are only registered in primary care[53]. The prevalence of hypertension in our cohort from study IV was slightly higher than that of other studies[23,44], likely because of differing exclusion criteria.

3.7 STATISTICAL METHODS

3.7.1 Considerations when choosing a statistical test

The choice of statistical method, for both descriptive and inferential statistics, depends on the type of variable - categorical or numerical - and which type of scale the variable is measured on – nominal, ordinal, or continuous (interval/ratio). The variable type is, for the sake of simplification, often referred to by type of scale it is measured on. Categorical variables can be measured on a nominal or an ordinal scale. Variables where the values have no inherent rank are measured on a nominal scale. Examples are sex, country of birth, and hair color. If the values of the variable can be ranked, it is measured on an ordinal scale. Examples are CHA_2DS_2-VASc score or education level. Numerical values can be measured on a ratio or interval scale. Examples are temperature, weight, age, and height. On a ratio scale there is an absolute zero, as for weight and height, and there can be no negative values. This allows a meaningful ratio to be calculated, i.e. a person who is 40 years old is twice the age of a 20-year old. Temperature in Celsius is measured on an interval scale, and similarly to the ratio scale each step is equidistant. An increase from 20 to 21 degrees Celsius is the same as an increase from 25 to 26.

3.7.2 Statistical tests in our studies

In our studies, nominal variables were descriptively presented in tables as proportions or frequencies; ordinal variables as medians with interquartile range; and numerical variables as means with standard deviation if the data was normally distributed. We compared two groups statistically using two sided test of proportions (pr-test) or the Chi^2-test for nominal variables with only two values (dichotomous or binary). When comparing two groups with respect to nominal variables with more than two values or ordinal variables, we used the Chi^2-test. For ordinal values, a Mann-Whitney test could have been used (and was used in some new analyses included in this thesis) instead of the Chi^2-test. For numerical variables we used the student's t-test to compare means between groups, granted that data was normally distributed.

Our main outcome variable in all the studies was medication dispensation. Medication dispensation was defined as a dichotomous variable, i.e. the only data values for the variable were "1" or "0". Because the outcome variable was dichotomous we used logistic regression. With logistic regression you can input multiple variables in the statistical model, and thus control for confounding. This is not possible with the pr-test or Chi^2-test. For a more detailed discussion on the choice of confounding variables used in the models, please see the methods sections in the included manuscripts I-IV.

3.7.3 What are odds ratios?

Logistic regression, which was used in all our studies, provides results in the form of odds ratios. Thus, it is important to understand what an odds ratio (OR) is. Imagine a cohort study which wishes to examine the association between an exposure, in this example smoking, and some form of cancer. In the 2x2 table in figure 8, the exposure and outcome data are presented. What are the odds of a smoker getting cancer? Odds are defined as the probability (p) of an event occurring, divided by the probability of it not occurring (1-p). In this case the probability (p) of a smoker getting cancer is 5/100. The probability of a smoker not getting cancer (1-p) is 95/100. Using the definition of odds, it follows that the odds of a smoker in the study getting cancer is (5/95)/(95/100)=0.053. It also follows that the odds of a non-smoker getting cancer is (20/800)/(780/800)=0.026. The OR is the odds of a smoker getting cancer, 0.053, divided by the odds of non-smokers getting cancer, 0.026. Thus, the OR is 0.053/0.026≈2. An odds ratio of 2 in this example means that smokers have a twice the likelihood of getting cancer, compared to non-smokers.

	Cancer (+)	Cancer (-)	Total
Smoking (+)	5	95	100
Smoking (-)	20	780	800
Total	25	875	900

Figure 8. How to calculate the odds ratio. Example of exposure and outcomes in a prospective cohort study aiming to study the association between smoking and cancer.

3.7.4 Missing data

There was no obvious problem with missing data in the studies in this thesis. In study III and IV, mosaic data was missing in around 0.3% of patients. For some of the primary care variables, there were missing values in 0.3-1% of patients. In study I, information on education was not available in 6% of patients.

3.8 ETHICAL CONSIDERATIONS

3.8.1 Informed consent

The Helsinki Declaration of ethical principles for research involving human subjects was first adopted in 1964 by the World Medical Association and has since been amended several times, most recently in 2013[182]. An important principle in the declaration is that of informed consent. The declaration states that all human subjects who take part in research and are capable of giving consent must give their informed consent to their participation. This means that research on human subjects must be voluntary. In large scale registry research it is often not possible, or at the very least incredibly impractical to obtain informed consent[183].

Our publications I-IV all included >10 000 patients (table 1). Our data set in study III and IV contained 108,806 patients before we applied exclusion criteria. There would be several problems with obtaining informed consent in this group of patients[183]. First of all it would be

very costly. Second, the practical difficulty of sending out letters containing information material and consent forms to hundreds of thousands of participants would be immense. Thirdly, requiring informed consent would lead to selection bias since the study would likely lose a considerable portion of the intended cohort. In the case of stroke, patients with cognitive difficulties may have a difficult time understanding information, and thus have difficulties giving informed consent. They may also have practical difficulties such as motor skill deficits which might make mailing signed consent forms more difficult. Stroke patients are a vulnerable group, which makes it all the more important to include them in a study. Losing a large proportion of patients would make the interpretation of the study results more challenging, limiting the external validity. Finally, the mere acquisition of informed consent by the researcher may influence patients' medication use, making them more aware and likely to change their medication taking behavior.

The basis for registry/database research being ethically acceptable despite the lack of informed consent is that data in registries/databases is anonymized. This was the case in all our studies. Data in the national healthcare registries and VAL is collected routinely, and collection is not influenced by research purposes. With anonymized data, the researcher cannot identify any individual in the study. If a study for some reason requires that a patient be identified, informed consent must be sought and acquired.

In publication I, we cross-linked data from VAL with data from SCB. The cross-linking was performed at the NBHW. Thus, they must have a linkage key, which can identify patients and thereby permit the cross linkage. It is important to note that the researchers do not have access to the linkage key. Furthermore, linkage keys are destroyed if keeping them is not specially requested by the researchers. The ethics of this cross-linking of data I believe are solid, granted that the NBHW keep the linkage keys safe until they are destroyed. In publications II-IV we only used unidentified data from the VAL database, and no cross-linking was performed.

3.8.2 Personal integrity and the potential for identification in study III-IV

In publications III and IV, there was a miniscule, but real, risk of patient confidentiality being breached, despite data in the primary care quality reports being anonymized and on a group level. The centers received data on medication use in their own stroke/TIA and atrial fibrillation patients. In very small primary care centers, there may have been a chance of the doctor identifying an individual patient's medication use. However, for a patient to learn that they have been identified from the quality reports, it would require that a doctor give some indication of this identification in a patient consultation. Although it would seem unlikely on the doctor's part, it may of course occur. If a patient's confidentiality is breached, it may be construed by an individual patient as a breach of their personal integrity. How big was the problem in our study? In the cohort of patients in study III with previous ischemic stroke/TIA there were only four out of approximately 100 intervention centers with <10 ischemic stroke/TIA patients listed. These centers had nine, eight, seven, and four patients, respectively. Patients are easier to identify if the pattern of medication use in a center is "all

or nothing" – i.e. if all the patients in a center are, or are not, using a medication. If there is a mixed pattern of medication use with some patients using and others not, then identification of the individual patient becomes harder. The mixed pattern of use was more common in these smaller centers.

We could have chosen to exclude all centers with <10 ischemic stroke/TIA patients. However, we felt that the overall positives in sending quality reports to all centers outweighed the negatives. Had some centers not received the reports this may have been construed as unjust and undermined the overall sympathy towards the "Quality Report Stroke" project. Furthermore, however disconcerting to the patient, the nature of the patient data which was at risk from a confidentiality breach cannot be considered as sensitive. The only data at risk was one variable, medication use, possibly in only one class of medication. A breach would have been more worrisome, had more data been included in the reports. Trying to be fair and wanting to supply quality data to all centers, together with the very small number of patients at risk of a confidentiality breach, led us to send the intervention to all centers in the intervention group. From a consequence ethics perspective, we believed this course of action was most sound.

3.8.3 Depriving control centers of quality data

According to a rights based ethics point of view, it may be argued that it was unethical to not supply quality data to all primary care centers in Region Stockholm, since they may be of value to patients in those centers. We, as researchers, believed that the intervention had the potential for improving patient outcomes, but we had no data to support this. Thus, launching a ubiquitous campaign with quality reports with an unknown effect would have been irresponsible towards tax payers. The resources that funded the quality reports could and should of course have been used elsewhere if the intervention was not beneficial. Thus, the main reason for it being ethical to withhold an intervention to a control group, in ours and in other studies, is that the effects of the intervention are not known. Moreover, to alleviate the absence of a potentially beneficial intervention in control centers, we sent quality reports to all primary care centers in Region Stockholm in 2017. This allowed all centers access to their quality data.

3.8.4 The integrity of primary care doctors

Potentially, the reports could have induced a feeling of "being watched" in the primary care center doctors. Receiving data their patients may have offended them, particularly if their patients happened to not be treated adequately. The concept may be viewed as a breach of some form of professional integrity. The consequences of this type of breach, I believe, are small when contrasted to the potential breach of patients' personal integrity.

3.8.5 Ethical permits

The studies in this thesis were approved by the regional ethics committee in Stockholm. The following ethical permits were acquired: 2007/784-31/4 (study III and IV); 2010/1158-31/2

(study I, III and IV); 2015/803-31/5 (study II); supplementary permit 2016/1547-32 (study II); clarifying permit 2011/662-39 (study III and IV); clarifying permit 2016/1048-32 (study III and IV); and supplementary permit 2016/1048-32 (study III and IV).

4 RESULTS

4.1 MEDICATION USE AFTER ISCHEMIC STROKE/TIA (STUDY I AND III)

4.1.1 Medication use 9-12 months after ischemic stroke/TIA

Use of statins 9-12 months after ischemic stroke/TIA was low in study I (diagnosis 2006-2010) for both men, 49%, and women, 39% (table 2). In unpublished results, this contrasted to the use of antiplatelets which was high, 75% for men and 74% for women (table 2). The use of anticoagulants in patients with atrial fibrillation was low (table 2), for both men (42%) and women (32%). In an unpublished analysis, the sex difference in anticoagulant use was mainly due to women in the ≥80 age group being undertreated (28% men, 22% women). In the ≥80 group, the sex differences were statistically significant in a multivariate logistic regression analysis (unpublished), even after adjusting for income class, which likely was a confounder of the association (change in the OR of 8,6% when adjusting for income class).

	Study I 2006-10				Study III 2016-17			
	Total	Women (%)	Men (%)	p	Total	Women (%)	Men (%)	p
Medication class								
Statins	44	39	49	<0.0001	66	60	72	<0.0001
Antihypertensives	68	69	67	0.03	77	76	77	0.48
Anticoagulants	37	32	42	<0.0001	86	86	86	0.50
Antiplatelets	74	74	75	0.13	82	82	82	0.36

Table 2. Partially unpublished results. Comparison of sex differences in use of secondary preventive medication in patients with previous ischemic stroke/TIA in study I and III. Patients in study I had their ischemic event 2006-10 and patients in study III 2011-15. Medication use in study I was defined as one dispensation 9-12 months after the event and in study III as two dispensations in an 18-month period 2016-17. Differences tested with test of proportions/pr-test. Study I included 19 335 patients and study III 12 766 patients. Anticoagulants in patients with atrial fibrillation, antiplatelets in patients without atrial fibrillation.

4.1.2 Medication use after ischemic stroke/TIA over time

The use of all classes of secondary preventive medications after ischemic stroke/TIA have increased over time over time when comparing data from study I and study III (table 2, partially unpublished results). The increase is most pronounced for anticoagulants and statins.

4.1.3 Sex differences in medication use after ischemic stroke/TIA

When comparing temporal differences in medication use with respect to sex (table 2, partially unpublished results), use of all medication classes has increased for both men and women.

4.1.3.1 Anticoagulants

The differences seen between women and men in study I for anticoagulants can no longer be seen in study III (table 2). Also, when analyzing all included patients with atrial fibrillation in

study III, there are no longer any statistically significant sex differences in anticoagulant use in any age group (appendix table A1, unpublished results).

4.1.3.2 Statins

Contrastingly, the differences in statin use are still present in study III, albeit with both sexes increasing their use (table 2). These sex differences in statin use in study III, can still be seen when performing multiple logistic regression analyses, and adjusting for comorbidities, socioeconomy, and age (unpublished results). In the fully adjusted model the OR was 0.60 (95%CI 0.55-0.65) with an OR <1 meaning that women use less statins (unpublished results). Finally, statistically significant sex differences in statin use can be seen in all age groups (Appendix table A2, unpublished results).

4.2 SOCIOECONOMY AND MEDICATION USE (STUDY I)

Socioeconomic variable		Anti-hypertensives (OR) [95% CI]	Statins (OR) [95% CI]	Antiplatelets (OR) [95% CI]	Anticoagulants (OR) [95% CI]
Age group	19-64	0.54 [0.50-0.59]	0.85 [0.79-0.92]	0.69 [0.63-0.76]	1.59 [1.26-2.00]
	65-79	reference	reference	reference	reference
	>80	1.11 [1.02-1.20]	0.45 [0.41-0.48]	0.98 [0.89-1.08]	0.38 [0.33-0.44]
Sex	Men	reference	reference	reference	reference
	Women	0.96 [0.90-1.02]	0.77 [0.72-0.82]	0.92 [0.85-1.00]	0.93 [0.80-1.07]
Income	Highest	1.03 [0.94-1.12]	1.35 [1.24-1.47]	1.16 [1.04-1.29]	1.55 [1.28-1.87]
	3rd quartile	1.06 [0.96 – 1.17]	1.18 [1.07-1.30]	1.09 [0.96-1.23]	1.37 [1.11-1.69]
	2nd quartile	reference	reference	reference	reference
	Lowest	1.00 [0.85-1.18]	0.84 [0.72-0.99]	0.79 [0.66-0.95]	0.93 [0.64-1.35]
Education	High	0.89 [0.82-0.96]	1.03 [0.95-1.11]	0.90 [0.82-1.00]	1.01 [0.85-1.21]
	Medium	reference	reference	reference	reference
	Low	1.10 [1.02-1.19]	0.90 [0.84-0.97]	1.04 [0.95-1.15]	0.85 [0.73-1.01]
Country of birth	Sweden	reference	reference	reference	reference
	Nordic	1.10 [0.97-1.24]	0.97 [0.86-1.09]	0.90 [0.78-1.04]	0.97 [0.74-1.28]
	Europe	0.87 [0.77-0.99]	1.02 [0.90-1.16]	0.96 [0.82-1.13]	0.87 [0.64-1.18]
	Outside Europe	0.69 [0.58-0.81]	1.05 [0.89-1.24]	0.80 [0.66-0.97]	0.94 [0.56-1.56]

Table 3. Partially unpublished results. Based on data from study I. Multivariate analysis of association between medication use 9-12 months, after ischemic stroke/TIA diagnosis 2006-10, and socioeconomic and demographic factors. Antiplatelets in patients without atrial fibrillation. Anticoagulants in patients with atrial fibrillation. Adapted from Geary et al. *Sociodemographic factors are associated with utilisation of statins after ischaemic stroke/TIA.* International Journal of Clinical Practice Mar 2017;71.

In study I, statin use was low (44%). Thus, statins became the focus of the study. However, we studied the use of all recommended secondary preventive medications 9-12 months after ischemic stroke/TIA (antiplatelets in patients without atrial fibrillation, anticoagulants in patients with atrial fibrillation). In the partially unpublished multivariate analysis in study I (table 3), education, income, sex, and age were associated with statin use 9-12 months after ischemic stroke/TIA. Patients in the lowest education class were less likely to use statins than patients in the medium class. Patients in the two highest income classes were more likely to use statins than patients in the second lowest income class, who in turn were more likely to use statins than patients in the lowest income class. Patients in the age group 65-79 were more likely to use statins than both patients of lower and higher age. Men were more likely to use statins than women.

Patients in the highest income group (and second highest for anticoagulants) were more likely to use antiplatelets and anticoagulants, than patients in the second lowest income group. Patients in the youngest age group were more likely to use anticoagulants, and the eldest age group (≥80) less likely, compared to patients aged 65-79. Low education was associated with using more antihypertensives. Patients born in Europe outside of the Nordic countries were less likely to use antihypertensives. Patients born outside Europe were less likely to use both antihypertensives and antiplatelets.

I performed a new multivariate analysis (unpublished results) on the dataset from study I, focusing only on statin use in ischemic stroke patients (Table A3 in appendix). This analysis did not differ much from the original one (table 3). The new analysis was performed to allow for comparison with another Swedish publication[184] which studied socioeconomy and statin prescription after ischemic stroke.

4.3 ANTICOAGULANT USE IN ATRIAL FIBRILLATION (STUDY IV)

4.3.1 Anticoagulant use over time

Anticoagulant use in patients with atrial fibrillation has increased from 2014-15 to 2016-17 in Region Stockholm. In atrial fibrillation patients with CHA_2DS_2VASc score ≥2, 77% of men and 75% of women used anticoagulants in 2014-15, 83% of men and 81% of women in 2016-17. In unpublished results, the increase has likely been largest in the age group ≥85, where anticoagulant use increased from 71% to 79% (appendix table A4).

4.3.2 Age differences

There were some age differences in the use of anticoagulants in patients with atrial fibrillation, with the highest proportion of treated patients being in the age group ≥65 (unpublished results, table A4). The proportion of patients who used anticoagulants in the youngest age groups, 18-54 and 55-64, depended on how the CHA_2DS_2VASc score was used to include patients (table A4). For example, in 2016-17, 65% of patients aged 18-54 with CHA_2DS_2VASc ≥2 used anticoagulants, and 75% of patients if the CHA_2DS_2VASc score was ≥2 in men and ≥3 in women (table A4).

4.3.3 Sex differences

In supplementary table 6 in study IV, a multivariate logistic regression model showed that women with atrial fibrillation diagnosis in 2011-15 were less likely to use anticoagulants than men in 2016-17. In an unpublished analysis, characteristics between women and men with an atrial fibrillation diagnosis in 2011-15 differed somewhat (appendix table A5). Women were older than men and had a lower prevalence of diabetes, heart failure, hypertension, and previous myocardial infarction. Fewer women than men were treated with statins. Anticoagulant use was 83% in men with CHA_2DS_2VASc score ≥2, and 82% in women with CHA_2DS_2VASc score ≥3 (unpublished data). Patients with CHA_2DS_2VASc ≥2 for men and ≥3 for women were further analyzed with multivariate logistic regression with the same adjustment models used in the original publication (unpublished analysis). The sex differences were no longer statistically as the 95% confidence interval included 1 - OR 0.93 (95% CI, 0.87-1.00). Sex differences in the youngest age groups depended on which CHA_2DS_2VASc scores were used to include patients (table A4). In the age groups ≥65, the absolute sex differences in use of anticoagulants in 2016-17 were small, and there were no statistically significant differences (table A4).

4.4 DIAGNOSIS RECORDING (STUDY II-IV)

4.4.1 Study II

Diagnosis recorded patients were more likely to use statins in both ischemic stroke (OR 1.58, CI 1.42-1.76), TIA (OR 1.53, CI 1.28-1.82), and ACS (OR 1.64, CI 1.47-1.83). The association was even stronger when studying antithrombotics. Both recorded men and women were more likely to use statins and antithrombotics. For antihypertensives the pattern of the association was more unpredictable. Men with a recorded ischemic stroke diagnosis were more likely to use antihypertensives, whereas women with a recorded TIA diagnosis were less likely.

4.4.2 Study III and IV

4.4.2.1 Diagnosis recording of ischemic stroke/TIA (study III)

Diagnosis recording of patients with ischemic stroke or TIA increased over time from dispensation period A (2014-15) to B (2016-17), but the absolute proportions of diagnosed patients were still low, particularly for TIA (table 4, partially unpublished analysis). Patients in intervention centers with TIA were statistically more likely to be recorded than patients in control centers after, but not before, the intervention. The absolute differences were small. For ischemic stroke, there were no statistically significant differences in diagnosis recording between control and intervention center patients before, or after, the intervention (table 4, partially unpublished analysis).

	Intervention centers (%)	Control centers (%)	p	All Centers in Region (%)
TIA (Study II & III)				
Dispensation period A (n=5 577)	10	11	0.66	
Dispensation period B (n=5 473)	18	16	0.02	
Study II (n=4 214)				16
Ischemic stroke (Study II & III)				
Dispensation period A (n=8 174)	34	34	0.50	
Dispensation period B (n=7 796)	44	43	0.53	
Study II (n=6 295)				44
Atrial fibrillation (study IV)				
Dispensation period A (n=29 948)	68	68	0.82	
Dispensation period B (n=31 477)	74	72	0.001	

Table 4. Partially unpublished results, based on data from studies II-IV. Proportion of patients with a recorded diagnosis in primary care in Study II and during dispensation periods (A=140701-151231, B=160101-170630) in studies III and IV. By intervention status (for study III and IV) and diagnosis. Patients with atrial fibrillation had a CHA_2DS_2VASc score ≥2. For study III and IV, index diagnosis 2009-14 (A) or 2011-15 (B). For data on methodology used for diagnosis recording in study II please see original publication or other sections of this thesis. Differences tested with Chi^2-test.

4.4.2.2 *Erratum in study III*

Due to a programming oversight, which only affected the results for diagnosis recording, the absolute numbers for TIA and ischemic stroke recording were too low in the supplementary material in study III. The correct numbers can be seen in table 4. We also reported in study III that there was a statistically significant difference in diagnosis recording of TIA between intervention and control centers after, but not before, the intervention. In the corrected analysis the odds ratios for the associations have changed slightly, but showed the same overall results. A correction, with the new analyses, has been sent to Acta Neurologica Scandinavica.

4.4.2.3 Diagnosis recording of atrial fibrillation (study IV)

Diagnosis recording for atrial fibrillation patients with CHA_2DS_2VASc ≥2 was significantly higher than in patients with ischemic stroke or TIA (table 4, unpublished analysis). There were slight, but statistically significant differences between intervention and control centers in diagnosis recording after, but not before, the intervention.

4.4.2.4 Characteristics of diagnosis recorded and non-recorded patients

In a new analysis of data from study III, I compared characteristics of recorded and non-recorded patients with ischemic stroke. Recorded patients were more likely to be men, and

used more statins, antihypertensives, and antiplatelets (appendix table A6). Recorded TIA patients used more statins and antiplatelets; were slightly older; and had less atrial fibrillation and diabetes (table A6).

In another new analysis of data from study IV, I compared characteristics of recorded and non-recorded patients with atrial fibrillation and a CHA_2DS_2VASc score of ≥2 (appendix table A7). Recorded patients were older; had higher CHA_2DS_2VASc scores; used more antihypertensives and statins but less antiplatelets; had lower prevalence of previous myocardial infarction; but a higher prevalence of heart failure and hypertension. Recorded patients used anticoagulants to a much higher degree (92%), than non-recorded patients (54%).

4.5 THE AUDIT & FEEDBACK INTERVENTION (STUDY III AND IV)

4.5.1 Study III

The audit & feedback intervention showed neutral results on medication use in patients with previous ischemic stroke/TIA (table 4 in study III). A sensitivity analysis defining medication use as 2-6 dispensations in the 18-month dispensation period was performed and did not change the results (supplementary material in study III). Also, two sub-group analyses were performed, neither of which showed any effect of the intervention (supplementary material in study III). One of these subgroup analyses compared intervention centers that potentially used the reports, and the control centers. The other compared the centers that may have used the reports with the other intervention centers.

4.5.2 Study IV

In the multivariate logistic regression analysis, patients with atrial fibrillation in intervention primary care centers were more likely to use anticoagulants than control center patients after, but not before, the intervention. However, when comparing odds ratios before and after the intervention, differences were small (table 2 in study IV). Also, the absolute differences were small. The before-after proportion of patients using anticoagulants was 76-81% in control centers and 77-83% in intervention centers. In an analysis including only women, intervention center patients were more likely to use anticoagulants after, but not before, the intervention (table 3 in study IV). The difference in odds ratios before and after the intervention was slightly larger than in the main analysis. However, similarly to the main analysis, absolute differences between intervention and control center patients were small. Before the intervention, 74% of women in control centers and 75% in intervention centers used anticoagulants (unpublished results). After the intervention those same proportions were 80% for control center patients and 82% in intervention centers (unpublished results).

Similarly to the analysis in study III, a sensitivity analysis of different number of dispensations defining medication use, did not change the results (supplementary material in study IV). The same two subgroup analyses as in study III were performed, neither showing any clear effect of the intervention (supplementary material in study IV). Also, patients ≥75

years of age were specifically analyzed and results were similar to the main analysis (supplementary material in study IV). Finally, results were nearly identical to the main analysis if inclusion criteria were a CHA_2DS_2VASc score of ≥2 for men and ≥3 for women (unpublished data).

5 DISCUSSION

5.1 SOCIOECONOMY, DEMOGRAPHY, AND THE USE OF STATINS

5.1.1 Main results for all medication classes

In study I, we found that higher income was associated with using more statins, antiplatelets, and anticoagulants (in patients with atrial fibrillation and stroke) 9-12 months after an ischemic stroke/TIA in 2006-10. Patients in the youngest age group (18-64) used less of all medication classes except anticoagulants, which were used more. Low education was associated with using less statins but more antihypertensives. The variable "country of birth" was hard to analyze and interpret as the groups were large and heterogeneous, for example "outside Europe". Women used less statins.

5.1.2 Focus on statins and income

Statins are the secondary preventive medication class which is used the least. Anticoagulants were also used sub-optimally in study I. However, it has become clear that anticoagulant use has increased significantly from the numbers we reported in study I. Thus, given that antihypertensives, antiplatelets, and anticoagulants show a relatively high level of use, any socioeconomic differences are likely to be most important for statins. Thus, I have chosen to focus on statins in this discussion, and income in particular, since the association between statins and income showed a clear stepwise gradient in study I.

5.1.3 Other Swedish studies of statin use

5.1.3.1 Prescription and adherence and the association with socioeconomy and demography

Two other Swedish registry studies have studied socioeconomic factors and statin use after ischemic stroke[51,184]. One of the studies focused on factors associated with prescription of statins at discharge[184], and the other on factors associated with two-year adherence in all patients prescribed a statin at discharge[51]. I performed a new (unpublished) analysis using the dataset from study I (table A3), including only the patients with ischemic stroke. The new analysis showed that many factors associated with statin use in our study at 9-12 months, were also associated with statin prescription at discharge[184]. Being female was associated with both lower prescription at discharge and lower use after 9-12 months. High income and high education were associated with higher prescription and use after 9-12 months. Contrastingly, prescription was lower in the 70-79 age group compared to the 18-59 group, while statin use after 9-12 months was higher. Both prescription and medication use after 9-12 months were lower in the ≥80 age group. The study of statin adherence[51] found that women were less adherent and also that higher out of pocket costs were associated with lower adherence[51]. Higher income was associated with better adherence to statins, but the association was not statistically significant on multivariate analysis[51].

5.1.3.2 Relevance of comparing prescription, medication use, and adherence?

Prescribing; medication use in all patients in a certain time period (study I); and adherence are different outcomes. For prescribing, all patients with ischemic stroke were studied[184], as was also the case in study I. In the study of statin adherence only patients who were prescribed statins were studied[51]. The factors associated with doctors choosing to initiate treatment after stroke may differ from factors associated with patients using the medication in the long term. An example of this is that patients born in Sweden were less likely to receive a statin prescription[184], but more likely to be adherent[51]. Thus, while it may be interesting to compare socioeconomic and demographic factors that influence prescription, medication use, and adherence, any direct comparisons should be interpreted with caution.

5.1.4 Income and statin use in other settings

5.1.4.1 Income may be associated with regimen persistence in ischemic stroke/TIA

International studies on the association between income and statin use after stroke specifically are lacking. Bushnell et al studied persistence and adherence to a regimen of secondary preventive medications in patients with ischemic stroke/TIA in the US[58]. They found that patients having insurance and having an income that adequately met their household needs were associated with increased likelihood of being regimen persistent and adherent.

5.1.4.2 Income and statins in primary and secondary prevention of cardiovascular disease

Similarly to our study, other studies in varying populations in high income countries have described an association between higher income and better statin use. Studies of medication use in myocardial infarction patients in Canada and Denmark have shown an association between higher income and better statin use[185,186]. The same association has been seen in studies of primary prevention from Denmark and Finland[187,188]. One of the studies showed sex differences, with the association between income and statin use only being observed in men[187]. Studies with mixed primary/secondary prevention cohorts have found somewhat differing results[189-192]. Two studies, from Sweden and the US respectively, found higher income to be associated with better use of statins[189,190], while an Israeli and an Australian study found no such association[191,192]. The lack of association with income in the Israeli study is hypothesized by the authors to be due to the low level of co-payment[191].

Finally, studies on statin use from the US in both a mixed primary/secondary prevention cohort[193] and a coronary heart disease cohort[194], indicate that lower co-pay may be associated with higher use of statins[193,194].

5.1.5 Income associated with medication use in Sweden despite subsidies and cheap drugs

The fact that lower income is associated with lower medication use of several medication classes is somewhat surprising since medications are relatively cheap, and medicine is subsidized in Sweden[195].

5.1.5.1 Equivalized disposable income

The exposure variable "income" in study I was equivalized disposable income (EDI). EDI is a concept that was created to be able to compare the economic conditions of households with different compositions, i.e. single people; married people without children; married with a specific number of children etc[196,197]. The rationale is that there are advantages of cohabitating, in that consumption in the household becomes cheaper per capita. Thus, to be able to compare households, incomes are weighted. EDI is calculated as the sum of all positive income minus taxes (any potentially other negative transactions) in the household, and is then weighted by household composition[196]. The EDI in the lowest income quartile in study I was <108 000 SEK in 2009, and >200 000 SEK in the highest quartile.

5.1.5.2 Cheap medication costs with generic options 2007-2011

Simvastatin became generic before the start of the period of dispensation in study I[198], and the cost of a daily dose of simvastatin started at 50 öre (0,5 SEK) in 2009[199]. Aspirin is a medication that has been available for many years and is cheap. Currently 100 tablets of aspirin (Trombyl®) 75 mg costs 62 SEK[200].

5.1.6 Summary of the association of income and statin use after ischemic stroke/TIA in Sweden

The differences in statin use between income groups in study I remained after multivariate analysis with adjustment for potential confounders such as age group and sex. Sjölander et al also showed that higher out of pocket cost, i.e. the cost which was not subsidized, was associated with lower adherence to statins after ischemic stroke[51]. Taking into account the statistics on EDI, it still seems odd that patients would not be able to afford a statin, which would have cost no more than around 300-400kr/year. EDIs are not weighted for region, and Stockholm may be more expensive than other regions and thus may make income more important. In conclusion, taking into account both national and international studies, it cannot be excluded that income in itself may have been a factor which influenced statin use at the time of study I. However, it must be appreciated that other unknown factors related to income may have contributed to the association.

5.1.7 How is the awareness of income inequality useful?

Knowledge of income inequality in medication use is of limited use clinically, but may be useful in the planning of national medication subsidization. While there is no current evidence to suggest that reducing the level of co-pay would increase statin use in our setting, it is an interesting idea if income inequality persists in newer studies. Alternatives to the current system where subsidies start at 1100 SEK, could be to start subsidizing earlier, or from 0 SEK.

5.1.8 Are the socioeconomic associations dynamic over time?

Since medication use after ischemic stroke/TIA has improved considerably over time it is possible that the association between socioeconomic factors and medication use may also

have changed. Also, disposable income may change over time. The previously mentioned study on prescription and socioeconomy included patients in 2004-2009, when only 46% of stroke patients were prescribed statins[184]. In 2019 statins were prescribed to 81% of stroke patients[2]. The study on adherence and socioeconomy included patients from 2009-2010[51]. Repeating these studies against a baseline of higher mediation use would be interesting to see for example if income inequalities persist.

5.2 USE OF ANTIPLATELETS AND ANTIHYPERTENSIVES REMAINS HIGH

Use of antiplatelets and antihypertensives remains high in Region Stockholm. 82% of patients with previous ischemic stroke/TIA (without atrial fibrillation) use antiplatelets and 77% use antihypertensives. When medication use is defined as five dispensations in 18 months it remains high, 68% using antiplatelets and 71% antihypertensives. For statins, medication use drops to 51% when defined as five dispensations (appendix table A8).

5.2.1.1 Antihypertensives – more complicated to interpret than the other classes

Antihypertensives are different than the other secondary preventive medication classes in that medication use was defined as two dispensations of *any* antihypertensive medication. With statins and antiplatelets the recommended daily dose will generally be just one tablet. Patients treated with antihypertensive treatment may be on one of many different medication regimens, which may change over time. Hypertensive patients often require more than one class of antihypertensive drug to treat their hypertension[201,202]. Furthermore, recent guidelines published in 2018 recommend that most antihypertensive patients requiring treatment should be started a combination of two antihypertensive drugs rather than monotherapy[202]. Consequentially, being dispensed antihypertensives twice in 18 months could mean several things. For example, a patient could have tried two different medications and then stopped using them. An example could be a patient trying an angiotensin converting enzyme (ACE) inhibitor, experiencing side-effects, switching to an angiotensin II receptor blocker (ARB) and stopping it because of more side-effects. Also, being dispensed four times during the 18 months could mean being on one medication at the start of the 18 months, and then being dispensed additional classes of antihypertensive medications during the rest of the period.

5.2.1.2 Measurable goals in antihypertensive treatment

Another way in which antihypertensives are different compared to most other secondary preventive medication classes, is that there are measurable hypertension goals for treatment which are applicable to most patients[15]. It is of course possible to measure blood low-density lipoprotein (LDL) levels as a marker of statin effect. While there may be LDL targets in the future in stroke[203], these are not yet established. Furthermore, recent guidelines support the use of statins in all patients, regardless of LDL level[204]. Contrary to LDL targets, a blood pressure target of <90 diastolic and <140 systolic are well established in secondary prevention of ischemic stroke/TIA[15,202].

5.2.1.3 High use of antihypertensives without reaching blood pressure targets

A large proportion of patients with previous ischemic stroke/TIA use antihypertensives. However, it is well established that many patients with hypertension with or without previous ischemic stroke do not reach treatment goals[65,205-207]. Thus, from a secondary stroke prevention perspective, dispensation data is not enough to determine how many antihypertensive medications the individual patient needs to be using to achieve blood pressure goals. Also, some patients may not be treated with antihypertensives since they have an optimal blood pressure. Future studies of antihypertensive treatment after ischemic stroke/TIA would benefit from utilizing data on blood pressure levels from primary care. It would be interesting to study the patterns of antihypertensive medication use in patients achieving and not achieving blood pressure targets.

5.3 STATIN USE STILL SUBOPTIMAL AFTER STROKE

5.3.1 Statin use in Stockholm is still suboptimal

Statin use after ischemic stroke/TIA has improved over time in Region Stockholm but is still not optimal. Study I and III are somewhat different methodologically but it is clear that statin use has increased, being 66% in III (ischemic stroke/TIA diagnosis 2011-15). The NBHW has set a target of ≥80% of patients using statins 12-18 months after ischemic stroke or TIA[18]. The target is defined as patients being dispensed statins at all in the time period 12-18 months. Thus, patients are still not optimally treated.

5.3.2 Age differences in statin use

While statin use is not optimal in any age group in the cohort of ischemic stroke/TIA patients diagnosed 2011-15 in Region Stockholm (study III), it seems to be highest in the 65-79 age group (table A2). Only 45% and 56% of patients aged 18-54 and ≥85, respectively, used statins. Thus, it seems that increasing statin use is most urgent in the youngest and the oldest.

5.3.3 Comparison with national Swedish data

Comparing with other Swedish data is difficult due to methodological and temporal differences[16,51]. Previous Swedish studies with national data have reported two-year statin adherence[51] and persistence[16], respectively, after ischemic stroke. Two years adherence, defined as a PDC of ≥80%, was 74%[51], while two-year persistence was 56%[16]. As previously mentioned in this thesis, it is hard to compare persistence; adherence; and multiple dispensations in a time period in all patients. However, it should be mentioned that, similarly to our study on medication use, adherence to statins was lowest in the 18-54 and ≥85 age groups[51].

5.3.4 Statin use internationally

There is room for improvement of statin treatment after ischemic stroke in Sweden, but other countries, regardless of continent, seem to be in greater need of improving statin use[10,16,34,43,51,57-59,65,90-92,208,209]. I performed a literature search in August 2020, which

identified 16 studies reporting on the use of statins after ischemic stroke/TIA (appendix table A10). Six of them, including study I and III, are from Sweden. The studies on statin use are generally of high quality, and are not subject to all of the limitations affecting studies on other medication classes, as previously mentioned in section 1.4.2.5. However, similarly to what was described in the background section, studies are heterogeneous with regard to method for studying medication use; duration of follow up; geographical area; and time period. As has previously been discussed in this thesis it is important to know what is being studied - adherence, persistence, or medication use in all patients. The study of persistence or adherence does not all include all patients, only those who have started treatment.

Of the ten international studies, five focused on persistence, one on adherence and four on medication use in all patients (table A10). Persistence ranged from 38-76%, the highest number seen in a US study, where participating hospitals were involved in an "improving stroke care"-program (Get With The Guidelines Stroke)[58]. The only study using adherence as an outcome found 66% of statin users to be adherent[90]. Medication use of statins ranged from 8-60% in the four identified studies, where the lowest use was seen in a Chinese cross-sectional community study[208]. The very low proportion of users (8%) likely reflects both sub-optimal care in China, and the duration of time after the index event when medication use was registered (median 48 months). It should also be noted that statin use in South America after stroke seems to be very low[209] with only around 10% of patients treated.

5.4 STATINS ARE STILL USED MORE BY MEN

5.4.1 Sex differences in statin use

Men use statins more than women after ischemic stroke/TIA in Region Stockholm. In patients with an ischemic stroke/TIA diagnosis 2011-15 (study III), 72% of men and 60% of women used statins. Multiple studies have shown that women with established, or at risk for, cardiovascular disease use statins less than men[184,210-214]. An American study of 6 000 patients in community practice reported sex differences in several interesting parameters of statin use[210]. These sex differences included women being less likely to have been prescribed a statin (67% vs 78%); less likely to use the recommended treatment intensity (37% vs 45%); more likely to have never been offered statins (19% vs 14%); and more likely to have discontinued their statin (11% vs 6%)[210].

5.4.2 Sex differences in statin use over time in Stockholm

The absolute proportion of patients in Region Stockholm with previous ischemic stroke/TIA using statins has increased over time for both sexes, yet the sex gap remains. The differences in statin use between men and women are both statistically significant, and clinically relevant, in all age groups.

5.4.3 Statins are equally effective in men and women

Men and women derive equal benefit from statin treatment, with lower rates of cardiovascular events seen with statin treatment[215,216]. The fact that both sexes benefit from

statins makes the difference in statin use seen between sexes both in Sweden and internationally all the more concerning.

5.4.4 Women are prescribed less statins after ischemic stroke in Sweden

In addition to being dispensed less statins in the long term after ischemic stroke, women are initially prescribed less statins than men. This prescribing difference has been consistent over time. A Swedish national study of all patients with ischemic stroke between 2004 and 2009 showed that men were prescribed more statins at discharge from hospital, 52% vs 41%[184]. In 2019, 81% of patients in Sweden were prescribed a statin after ischemic stroke, 88% of men and 70% of women[2]. The sex differences were most pronounced in patients ≥ 80 years of age[2]. Statin prescription in all ischemic stroke patients in the seven hospitals in Region Stockholm ranged from 72-83% in 2019[2]. There are no reasons to believe that the sex difference seen nationally would be absent in Stockholm.

5.5 REASONS FOR SUB-OPTIMAL STATIN USE

5.5.1 Reasons for sub-optimal statin use in general

5.5.1.1 Side-effects

Statins can produce muscle related side-effects[217] which are often given as a reason for stopping statin therapy[218,219]. Thus, they may be an important reason for suboptimal statin use. Furthermore, muscle related side-effects seem to be more common in observational trials than in randomized controlled trials (RCT)[220,221]. This discrepancy between RCTs and observational studies may stem from the absence of a consistent definition of statin associated muscle symptoms, together with selective exclusion criteria in RCTs[220,221]. Although there are some exceptions[222], muscle related side-effects in RCTs of statins are relatively uncommon, with equal frequency in the statin and placebo groups[220,221,223,224]. For example, In the SPARCL trial of 80 mg Atorvastatin vs placebo in ischemic stroke patients the frequencies of muscle related side-effects over 5 years were 5.5% in the atorvastatin group vs 6% in the placebo group[224]. However, some observational studies have shown higher frequencies of muscular side-effects ranging from 8% to around 25%[218,225,226]. This relatively high frequency of side-effects may be important. Studies have shown that stroke patients are concerned about side-effects of medications[227], that concerns about medications is associated with higher non-adherence[78,79,83], and that the absence of side-effects may be a facilitator of good medication use[228].

5.5.1.2 Controversy surrounding benefit in the elderly

The benefits of statin treatment in the elderly has been questioned since studies on the secondary prevention of cardiovascular disease have often included very few older patients[229]. The definition of old is not always clear. Current ESC guidelines on the secondary prevention of cardiovascular disease recommend that old patients receive statins for secondary prevention of cardiovascular disease, but define “old” as patients ≥65 years[204]. A

meta-analysis from the Cholesterol Treatment Trialists' Collaboration (CTTC) in 2019 showed that older patients, ≥75 years of age, derive benefit from statins as secondary prevention, albeit with a trend towards lower effect for some outcomes than younger patients[230]. The available data on the effect of secondary prevention in elderly stroke patients is however still limited. In the CTTC study, the majority of secondary prevention patients had previous ischemic heart disease, and the authors do not specify if any patients with ischemic stroke were included[230]. Also, there is no specific data on the very old, ≥85, a group in which only 49% of patients with ischemic stroke/TIA in Region Stockholm 2011-15 were treated. Furthermore, patients in the SPARCL study which compared atorvastatin 80 mg vs placebo for the secondary prevention of ischemic stroke/TIA had a mean age of only 63[224]. To my knowledge there are no randomized studies in patients with prior ischemic stroke/TIA that have specifically studied older patients. In conclusion, while it may be reasonable to treat patients with previous ischemic stroke/TIA ≥75 years of age with statins, the risk/benefit in the very old is still unclear and individualization of treatment may be warranted. Individualization does not necessarily mean abstaining from treatment, but can also mean choosing to treat, but with lower doses of statins.

5.5.1.3 The nocebo effect and negative media coverage

The nocebo effect, i.e. the inverse of placebo, has been suggested as a contributor in suboptimal statin use[231,232]. Furthermore, negative media coverage of statins may increase the likelihood of patients discontinuing statins[233-235].

5.5.2 Reasons for sub-optimal statin use in women

5.5.2.1 Side-effects and beliefs?

The reasons for the lower statin use in women after ischemic stroke are not clear. Moderate to severe myopathy may be more common in men[236]. Possibly, women could have a higher total burden of muscle symptoms leading to them discontinuing their statin[218]. This is however speculative since there are conflicting studies[226]. It has also been suggested that women may have different beliefs concerning statins than men[210], thus potentially making them more likely stop treatment. Women may be less likely than men to believe that statins are safe (48% vs 55%) and that they are effective (68% vs 73%)[210]. Finally, one study showed that more women than men give side-effects as the reason for stopping a statin[218].

5.5.2.2 Non-prescription

Non-prescription at discharge after the index stroke may lead to enduring sex differences. The decision to treat with a statin is often made by neurologists or stroke specialists in hospital and may influence future prescription decisions in primary and secondary care.

5.5.2.3 Age differences

Finally, it must be noted that women with ischemic stroke/TIA are older than men and the very old are treated to a lesser degree with statins. A majority, 61% of patients in the ≥85 age

group with a previous ischemic stroke/TIA diagnosis in 2011-15, were women in study III (unpublished results).

5.6 BENEFICIAL INTERVENTIONS IN THE LITERATURE TARGETING STATIN USE

5.6.1 Several studies have shown benefit

A Cochrane systematic review of interventions aimed at increasing statin adherence found several potentially beneficial interventions[237]. Interventions with beneficial effects were those with "intensified patient care"; a fixed-dose combination strategy (FDC), also known as "poly-pill"; and an automated refill reminder intervention[237]. Secondary preventive studies included in the review (nine out of 35) focused mainly on ischemic heart disease[238-245]. Only two out of nine studies with mixed primary/secondary prevention stated proportion of patients with prior cerebrovascular disease[246,247]. The proportions were 13%[246] and 16%[247], respectively.

5.6.2 Fixed-dose combination interventions

Four out of five trials using FDC found better adherence in the intervention group than control group[238,246-248]. The FDC consisted of aspirin, a statin, and antihypertensive medication[238,246-249]. The treatment in the control groups were either usual care or the individual drugs[238,246-248]. The one study which did not report a positive outcome only studied proportion of patients discontinuing treatment[249]. The comparator was placebo, which may not be equivalent to a real life situation where poly-pills will likely be used instead of the individual components[249].

5.6.3 Intensified patient care interventions

Several studies using intensified care interventions reported benefit on statin use[240,241,243,250-259]. Interventions in the group "intensified patient care" were heterogeneous. They often involved pharmacists delivering patient feedback and information[243,250,252,259]. Two studies used short message service (SMS) reminders[240,257], and one provided calendar reminders for better medication use[255]. Another two studies had intensified follow up by telephone[241,254]. Two studies used automated phone calls to target patients who had not picked up prescriptions[251,258]. One study provided individualized risk factor profiles, and targets for improving risk profile, in context of increased nurse-led follow up at 3, 9, and 18 months following baseline[256]. Another study in primary care randomized patients to usual care or to education material and follow up visits every eight weeks for 48 weeks. Finally, one study used a multifaceted approach with education at discharge from hospital, primary care center contact, and structured pharmacist follow up at one week and one month[243].

5.6.4 Which of the beneficial interventions are useful for our purposes?

Many of the beneficial interventions require significant resources, thus limiting their application on a larger scale. Also, some interventions are based on monitoring an individual

patient's dispensations which is not possible in Sweden. Many studies involved pharmacist follow up, a function that, to my knowledge, is not practiced on a larger scale in Sweden. The interventions that seem most applicable to our setting are the use of a FDC strategy, and telephone and SMS reminders. How to incorporate such strategies in an intervention with the aim of increasing the total population use of statins is not obvious.

5.7 IMPROVING STATIN USE AFTER STROKE

This section summarizes some areas which could be targeted to improve statin use after stroke on a larger scale. An FDC strategy and/or SMS-reminders may have a role to play but are not mentioned further in this section.

5.7.1 Helping patients cope with side-effects

5.7.1.1 Information to patients regarding potential side-effects

Since side-effects are a common reason for discontinuation of statin therapy[218,219], helping patients to cope with them may be an important step in increasing statin use. A qualitative study revealed that patients feel that their concerns regarding side-effects are not always addressed by their doctors[227]. Thus, making sure patients feel informed of what side-effects may occur and how they can be handled could important.

5.7.1.2 Physician tools for handling side-effects

If side-effects do occur, there are structured strategies which may be applied by the clinician[260]. In the Region Stockholm online guideline resource for primary care, there is already a section on how to handle statin side-effects (www.viss.nu)[261], currently nested under the main subject of "hyperlipidemia". These guidelines for statin side-effects may need to be advertised more clearly and made even more easily accessible, possibly by creating a main subject entitled "statin side-effects".

5.7.2 Clinical decision support systems

Physician prescribing and motivating of patients could be targeted through a clinical decision support (CDS) system incorporated in the EMR. CDS systems in the context of medication use can work by giving the treating doctor a warning in the EMR when a patient with a certain registered diagnosis (e.g. ischemic stroke) is not being treated with a specific medication (e.g. statins)[106]. A prerequisite for CDS systems to work is that doctors can identify which patients the CDS system is applicable to. For this purpose, diagnosis recording in the EMR may become important.

CDS systems have, to my knowledge, not been studied specifically to improve utilization of statins in patients with previous stroke. CDS systems in an EMR have however shown potential in increasing the use of anticoagulants in atrial fibrillation patients in primary care[106]. CDS systems have also been studied with some promise in the primary care setting in

the context of statin use in diabetics[262], and in patients at high cardiovascular risk[263]. Interestingly, audit & feedback was a component of both studies.

5.7.3 Personalized patient feedback

The patient perspective is of course of importance and should be targeted. Personalized patient feedback may have a role to play[256,264], as is described in a systematic review on RCTs attempting to increase statin use in primary prevention[264]. Interestingly, a Swedish primary prevention RCT randomized patients in the intervention arm to view their own carotid ultrasound results[265]. This led to an increase use of self-reported statin use after 1 year, with a 9% absolute difference between intervention and control. Also, lower scores of cardiovascular risk (by Framingham risk score and SCORE) were seen in the intervention group. Although the results of this study are not applicable to secondary prevention, the concept of personalizing patient education and information, sometimes with visual aids, is attractive. In patients with ischemic stroke, where all patients are high risk, visual aids could include a visual representation of carotid ultrasound or computed tomography (CT) angiography of the carotid arteries and thus proving the concept of atherosclerosis as a chronic disease process to the patient. Furthermore, in another study (primary and secondary prevention cohort) with positive results on statin adherence, patients received "risk factor passports" with graphical presentations of their own 10-year risk for adverse cardiovascular outcomes[256].

5.7.4 Focus on sex differences with increased patient and physician awareness

Although not studied, to my knowledge, clinicians likely need to be made aware of the sex gap in statin treatment and the lack of evidence for treating men and women differentially. Speculatively, increased awareness may facilitate an increased statin prescribing and dispensing. An information intervention targeting both patients and physicians would be an interesting concept.

5.7.5 Benefit of lower LDL targets in stroke may increase treatment

Potentially, with the publication of the "Treat stroke to target"-trial showing benefit of a lower target LDL-level after TIA/stroke[203], even more guideline emphasis will be put toward statin therapy thus improving treatment.

5.7.6 Standardized care processes

Sweden is in the process of launching a national initiative for personalized and connected care processes in stroke/TIA ("Personcentrerat och sammanhållet vårdförlopp Stroke och TIA")[266]. Hopefully, this initiative will further improve the standards of care in ischemic stroke/TIA in Sweden, including reaching targets for medication use.

5.8 ANTICOAGULANT USE IN ATRIAL FIBRILLATION HAS INCREASED

5.8.1 All patients with atrial fibrillation

Anticoagulant use has increased from 2014-15 to 2016-17 in atrial fibrillation patients in Region Stockholm. The largest increase was seen in the group ≥85 years of age (71% to 79%). These results are consistent with other contemporary studies on atrial fibrillation patients in Stockholm[23,44].

5.8.1.1 Sex differences in anticoagulant treatment remain but are small

Sex differences in anticoagulant use in patients with atrial fibrillation in Region Stockholm remain but are no longer clinically relevant. Differences are small and have decreased over time which is consistent with another Region Stockholm study[23]. We aimed to study all patients with atrial fibrillation and a clear indication for treatment. The analysis is somewhat complicated by the divergence of local and international treatment guidelines during the time period of the study. If using international guidelines which state that treatment is indicated for men with $CHA_2DS_2VASc \geq 2$ and women $CHA_2DS_2VASc \geq 3$, then sex differences are even smaller than when all patients with $CHA_2DS_2VASc \geq 2$ are included. Also, differences may no longer be statistically significant.

5.8.2 Patients with ischemic stroke/TIA and atrial fibrillation

In the cohort from 2006-2010 (study I), only 37% of patients with atrial fibrillation used anticoagulants 9-12 months after ischemic stroke/TIA. In patients with previous ischemic stroke/TIA 2011-15 and atrial fibrillation (study III), anticoagulant use had increased considerably, with 86% of patients using anticoagulants. This is consistent with national prescription data from the RiksStroke registry where a steady increase in patients with atrial fibrillation being discharged with anticoagulants has been seen for the past 10 years[172]. In 2019, 80% of patients with atrial fibrillation were discharged with an anticoagulant[2]. The most common reason for withholding anticoagulants was that the physician adhered to instructions regarding contraindications, drug interactions, or caution (27%)[2]. The second most common reason was that the doctor wanted to start treatment after discharge (20% of patients not discharged with anticoagulant). Only 4% of non-treated patients declined treatment[2].

5.8.2.1 The sex gap in anticoagulant treatment after ischemic stroke/TIA has probably been closed in Stockholm

Similarly to statins, the use of anticoagulants in patients with ischemic stroke/TIA and atrial fibrillation has increased for both sexes. The sex differences in the use of anticoagulants that were seen after ischemic stroke/TIA in study I (42% of men, 32% of women treated with anticoagulants), could no longer be seen in study III. Sex differences in study I were largely caused by women ≥80 being treated to a lesser degree than men, 22% vs 28%. These sex differences in study I were to some extent confounded by differences in income. However, in study III there were no longer any statistically significant differences in anticoagulant use

between sexes in any age group. In particular, it seems that medication use has evened out between sexes in the ≥80 age group. It should be noted that there are still sex differences in prescription of anticoagulants after ischemic stroke on the national level in the ≥80 age group (75% women, 80% men)[2].

5.8.3 Reasons for increased anticoagulant use in Stockholm

5.8.3.1 Introduction of NOACs

The structured introduction of NOACs in Region Stockholm[56,267] meant that there was more focus on atrial fibrillation, both diagnosis and treatment, in general. During the period of NOAC introduction, the number of patients with an atrial fibrillation diagnosis increased substantially in Region Stockholm[23,44,56]. Also, marketing and educational activities from the pharmaceutical industry[267], and increased media spotlight on atrial fibrillation[23], may have been important contributors to increased anticoagulant use.

5.8.3.2 Risk of falls should not be a reason to withhold anticoagulation

Speculatively, studies downplaying the risk of falls as an important factor when choosing to anticoagulate patients with atrial fibrillation may have received increased attention during the structured introduction of NOACs. Risk of falling with a subsequent increase in the risk of bleeding is a common reason for withholding anticoagulant treatment[268]. However, the overall risk-benefit ratio for patients with atrial fibrillation at high risk of falls suggests that the risk of falls should not be a crucial factor in deciding whether or not to anticoagulate a patient[269,270]. One study estimated that a patient would have to fall approximately once every day (300 times/year) for the subdural hematoma risk from warfarin to overweigh the benefits of treatment[270].

5.8.3.3 Lower risk of bleeding with NOACs

A major concern of anticoagulant treatment is the risk of bleeding, with an intracranial location the most worrying. Studies have shown that NOACs are associated with a lower risk of major bleeding and intracranial hemorrhage[271,272] compared with warfarin. Thus, in patients judged to have an increased risk of bleeding, physicians could choose to treat with NOACs instead of warfarin which may have increased overall anticoagulant use.

5.8.3.4 Aspirin discouraged in atrial fibrillation treatment

National atrial fibrillation guidelines from the national board of health and welfare in 2013[273], discouraged from using aspirin at all in patients with atrial fibrillation. With less focus on aspirin, more focus could be put towards treating with anticoagulants. However, it should be noted that local guidelines in Region Stockholm[19] in 2012 still recommended aspirin as an option for patients with atrial fibrillation who could not be treated with anticoagulants. In 2013, the guidelines emphasized that aspirin is considerably less effective than anticoagulants at preventing stroke, but still recommended aspirin as an option. This recommendation remained in 2015.

5.9 DIAGNOSIS RECORDING IS ASSOCIATED WITH GREATER MEDICATION USE

Having a diagnosis recorded in primary care is associated with using more statins and antithrombotics in patients with previous ACS, ischemic stroke, and TIA. This association was also seen in study III for ischemic stroke and TIA. Nearly all recorded patients with atrial fibrillation and $CHA_2DS_2VASc \geq 2$ in study IV used anticoagulants, but only about half of patients without a recorded diagnosis. An audit and feedback intervention did not have any clear effect on diagnosis recording.

Diagnosis recording in TIA and ischemic stroke was similar in both study II and study III (after the intervention). It is debatable, and not yet known, which method is most suitable for defining diagnosis recording in primary care patients for these diagnoses. The method in study II has the advantage of standardizing recording to a certain duration of time (years 2 and 3) after an event. Patients with multiple diagnoses were however excluded, limiting the utility in a real life primary care context. In this sense, the methodology in study III and IV has advantages in that it gives a real life representation of how all patients with a previous diagnosis are recorded. Also, some patients in study III and IV will have had their index diagnosis/event four or five years before the recording period, which may better reflect long term practices in diagnosis recording.

Diagnosis recording in atrial fibrillation is considerably better than in patients with ischemic stroke, TIA, or ACS. The reasons for this are unclear. The higher diagnosis recording may be related to the fact that atrial fibrillation is, in general, a more commonly utilized diagnosis in primary care. It may be that atrial fibrillation is seen as an adequate diagnosis to input in the EMR than the other diagnoses, which may be more seen as acute events. Also, some patients with atrial fibrillation are only diagnosed and treated in primary care which may increase the likelihood of them receiving a primary care diagnosis[179]. Finally, treatment with anticoagulants requires extra attention from primary care which may increase the likelihood of an atrial fibrillation diagnosis.

5.9.1 Association and not causation

Having a diagnosis recorded in primary care is associated with greater medication use, but the causality is at present unclear. Physicians in primary care input their diagnosis in the electronic medical record after the patient encounter. The likelihood of a physician choosing to record a diagnosis is multifactorial and could be influenced by many factors - the doctor's prior knowledge of the patient; the patient's knowledge of their condition; patient comorbidities; the doctor's knowledge of the condition in question; the prior existence (or not) of the diagnosis in available medical records; the doctor's preferences and pattern of diagnosis selection; existence of a referral for the condition; financial reimbursement for recording[274] the diagnosis; local traditions in diagnosis recording; and potentially other factors. At this point in time, we do not know the characteristics of the doctors, patients, and surrounding factors which lead to a diagnosis being or not being recorded.

5.9.2 Potential mechanisms

Since non-recorded patients also use guideline recommended medications to a great extent, diagnosis recording is not a pre-requisite for treatment. Considering that it is difficult to know why certain doctors are more likely to diagnosis record, it is difficult to speculate in the mechanism of higher medication use in recorded patients. A potential mechanism could be that recording doctors have a greater knowledge of guidelines, or a greater interest in the condition in question. This would then, according to the theory, make them more likely to select a diagnosis and also to be adherent to existing diagnosis-relevant guidelines.

5.9.3 Potential future areas of use

Our study has shown that recording a diagnosis is associated with positive patient outcomes in the form of greater medication use. Medication use is, in itself, not a "hard outcome", but is associated with benefit to patients in the form of decreased risk of future cardiovascular events[31-37]. Although diagnosis recording has already been implemented as a quality indicator for many diagnoses by Sweden's "Quality in Primary Care"[159], the concept of diagnosis recording has not yet been studied enough to draw conclusions regarding its utility. To validate diagnosis recording as a quality indicator it would have to be studied and compared with other outcomes of care. It would be interesting to study outcomes such as preventable hospitalizations, which are often suggested as useful quality indicators[275], and mortality.

The use of diagnosis recording in general quality improvement may have great potential. For internal quality improvement purposes, a higher degree of diagnosis recording would allow for more accurate audit of quality, since more patients would be included in the audit. Also, if computer decision support systems are to be implemented, for example to improve medication use, diagnosis recording may be important. The electronic medical record (EMR) would need to identify to which patients the CDS system is applicable. Currently, this can only be achieved by a diagnosis being recorded in the EMR, since the EMR is not connected to the national patient registry. Thus, while not being ready to implement as a quality indicator in itself, diagnosis recording may still be useful for other interventions, and general quality improvement purposes.

5.10 AN AUDIT & FEEDBACK INTERVENTION DID NOT IMPROVE MEDICATION USE

5.10.1 Audit & feedback did not improve medication use in patients with ischemic stroke/TIA or atrial fibrillation

The audit & feedback intervention in study III and IV aimed to improve the use of secondary preventive medications in ischemic stroke/TIA patients (III) and anticoagulants in atrial fibrillation patients (IV). The intervention had either neutral (III) or small (IV) effects on medication use. Although there were small, statistically significant, differences between the intervention and control group in study IV after the intervention, the absolute differences were hardly clinically relevant. Control center patients increased their use of anticoagulants from 76 to 81% (5 percentage points), whereas intervention centers increased from 77 to 83%

(6 percentage points). Thus, I have chosen to discuss the reasons for the intervention not achieving better results.

5.10.2 Potential reasons for our neutral/small results

5.10.2.1 Predictors of effectiveness in audit and feedback interventions

Ivers et al[111] suggest the following factors that may predict the effectiveness of an audit and feedback intervention – (1) a low baseline performance; (2) a supervisor or colleague delivering the feedback; (3) >1 reminder; (4) feedback given in written and verbal form; (5) provides targets and an action plan.

5.10.2.2 The intervention in relation to predictors of effectiveness

We attempted to tailor our quality reports according to known success factors (2)-(5), but we do not know if the targeted doctors were able to appreciate these factors. The problem when assessing our intervention in relation to the predictors of effectiveness is that we cannot be sure if the intervention reached the intended targets, i.e. the primary care physicians. We targeted an intermediary, the primary care center directors, and depended on them disseminating the reports, and arranging internal meetings etc. This methodology has been used[144] previously but then in combination with practice site visits and network meetings. Many audit and feedback interventions target physicians directly[139,141,143,145]. If the primary care center director embraces the intervention, it may have a greater effect. If they do not, there will not be an intervention at all in that center. In our follow up questionnaire, only 25% of centers gave some indication that they used the reports. Thus, it is likely that our intervention did not achieve the desired level of dissemination among primary care doctors and then the predictors of effectiveness may not matter.

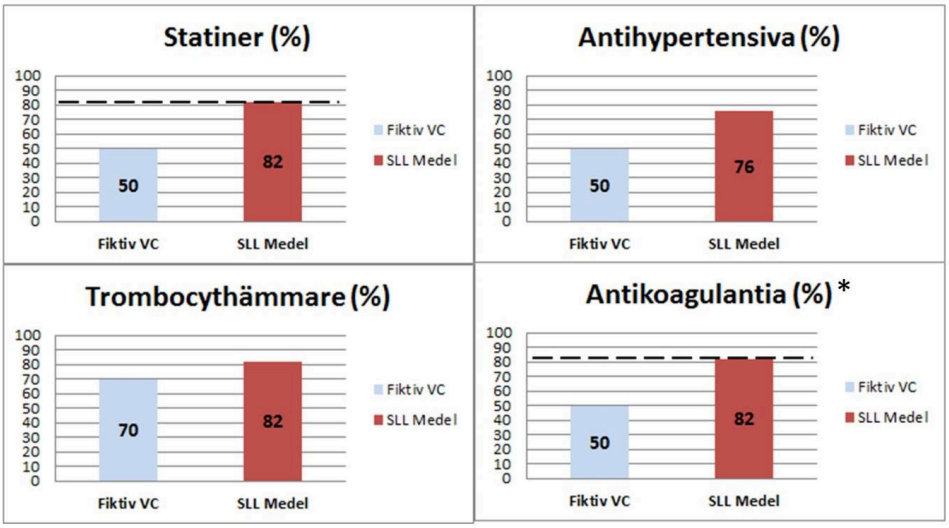
Regarding (1), which was out of our control, the baseline performance was relatively high in both study III and IV. In study III baseline performance before the intervention ranged from 63% for statins; to 76% for antihypertensives; to 82% for both antiplatelets and anticoagulants. In study IV baseline use of anticoagulants was 76%.

Kvalitetsrapport STROKE 2019

Fiktiv VC

Rätt medicinering förebygger stroke! Läkemedelsbehandling efter stroke/TIA är effektiv men andelen som behandlas varierar kraftigt hos listade patienter hos VC i SLL. År 2019 hade Fiktiv VC 200 listade patienter vilka haft tidigare ischemisk stroke/TIA. I nedan figur visas hur dessa patienter behandlas jämfört med landstingssnittet för VC i SLL, samt nationella målnivåer.

På Fiktiv VC kan behandlingen med statiner, antihypertensiva, trombocythämmare och antikoagulantia förbättras.



Figur 1. Läkemedelsanvändning hos patienter med tidigare ischemisk stroke/ TIA listade på Fiktiv VC.
*Hos patienter med förmaksflimmer
— — — — · Nationell målnivå från Socialstyrelsen

Figure 9. Page 1 of a potential alternative format of quality reports, with more emphasis on medication use in the figure. Third page includes action plan, see appendix for full quality report.

5.10.2.3 The format of our reports

The quality reports (appendix figure A1, de-identified version) contained a lot of written text and could, in retrospect, have been clearer regarding the current level of medication use at the centers. Also we could have related these medication levels to targets recommended by the NBHW[17,18]. We did provide current guidelines for how patients should be treated medically, but we did not provide an action plan as such on the reports. The action plan was only provided on one slide in the attached PowerPoint presentation. A different format for presenting data on medication use and diagnosis recording could have been chosen, such as that in figure 9 (for full four page quality report see appendix figure A2), which is a suggested alternative version of the quality reports. In this alternative report, more emphasis is put towards limiting text and graphically demonstrating medication use and diagnosis recording in the fictive primary care center "Fiktiv VC". Also, an action plan is provided (page 3, see appendix figure A2).

5.10.3 Could the intervention have been studied differently?

5.10.3.1 Longer follow up

Since our study outcome (medication use) was defined as two dispensations in an 18-month period, it is conceivable that any changes from an intervention would take time. The intervention was sent out in December 2015 to primary care center directors, but we do not know at what point in time there was an internal dissemination of our quality reports in the intervention centers. It is possible that the centers that actually used the reports, did so at some point in time during spring of 2016. If this was the case, then the intervention would only have had around 12 months to have a behavioral effect in doctors. It is possible that this time period is too short to discover potential effects of the intervention. We could have allowed more time to pass before analyzing medication use, for example analyzing medication use January 2017 – June 2018, and thus allowing a year for the intervention to have an effect.

5.10.3.2 Interrupted time series analysis

We could potentially have used a different study design utilizing interrupted time series analysis (ITS), which has become a popular tool for studying the effects of population based interventions[276]. It is being increasingly used in the study of medication use[277]. An ITS analysis study design is often selected in situations when randomization is not possible, like when an intervention targets an entire population[278,279]. For example, an Italian study from 2011 examined the effect of a smoking ban in public places on hospitalizations for ACS using ITS analysis[280]. The principle of an ITS analysis is that it predicts the trend of an outcome over time in a population, given that the intervention had not taken place[279]. This is known as the "counterfactual"[279]. This counterfactual trend is then compared to the actual observed trend. If the counterfactual differs from the observed trend, the intervention has likely had an effect.

Although ITS analysis is usually applied when analyzing the total population effects of an intervention, it is also possible to use when intervention and control groups has been defined, such as in our study III and IV[276,281]. Thus, we could have performed an ITS analysis on our dataset. Since the outcome in our studies is defined as a number of dispensations in a relatively long time period (18 months), it can be expected to change gradually following our quality report intervention. We would have had to follow the patient cohort for several years following the intervention. Our original dataset only included data for 18 months following the intervention. Any future analysis of the intervention, by our group or others, should consider defining being treated as 2 dispensations per year and then performing an ITS analysis on the years before and after the intervention.

An alternative study design for study III and IV could have been to send our intervention to all primary care centers in Region Stockholm. Then we could have used an ITS analysis in studying medication use of recommended medications after ischemic stroke/TIA and atrial fibrillation in the entire population of primary care patients. However, since this study design would not have included a control group, we would not have been able to determine the effects of competing interventions on the trends[276]. This would have been troublesome, since there was a lot of focus on atrial fibrillation in particular in Region Stockholm during the time of the study.

5.10.3.3 Following one cohort through both dispensation periods

We could potentially have chosen to follow stroke/TIA patients from index period A (2009-2014) across both the dispensation periods A (before intervention) and B (after the intervention. The analyses before and after the intervention would then have been in the same patients. I have performed such an analysis for all medication classes, after excluding the 186 patients (1.6%) who changed intervention status during the study (unpublished analysis). After performing multiple logistic regression analysis, adjusting for the same potential confounders as in study III, there was no effect of the intervention on any medication class. When studying only patients with atrial fibrillation diagnosis in 2009-14 in another unpublished analysis, results were similar to the analysis in the original publication (study IV).

5.10.3.4 A specific intervention for only diagnosis recording?

It would have been interesting to study an intervention focusing only on increasing diagnosis recording, without information on medication use. After such an intervention, outcomes such as medication use, recurrent ischemic stroke/TIA, and mortality could have been followed up. Currently we know that better diagnosis recording is associated with better medication use, but we do not know if increasing recording will increase medication use. For such a purpose it would be appropriate to not provide information on an intended outcome (medication use) in an intervention. A diagnosis recording intervention could be carried out in an entire region in Sweden, and studied with an ITS analysis.

5.10.4 Is audit & feedback useful in improving medication use after stroke?

Audit & feedback is potentially a useful tool, but may not be effective in our setting with high baseline use. Also, it is important to determine the reasons for patients not using medications in the long term. Are patients not using the medications because the doctors are not prescribing, or are existing prescriptions not being filled in the pharmacy? Also, it would be important to know the reasons for non-prescribing. Future interventions, audit & feedback or other, would benefit from knowing where the problem lies (doctor or patient) and thus could be better tailored to address it.

5.11 WHAT ARE REALISTIC TREATMENT GOALS AT A POPULATION LEVEL?

The NBHW states that 80% of patients with atrial fibrillation and ischemic stroke should be treated with anticoagulant, 85% for TIA[18]. The selection of a somewhat higher target level for TIA is explained in the guidelines by the fact that TIA patients are expected to experience fewer side-effects than stroke patients. Regarding statins, 80% of patients with ischemic stroke should be treated with statins, with the same recommendation for TIA. The rationale from the NBHW for the target not being 100% is that side-effects will make such a goal unattainable and there must be some room to operate. However, the rationale for selecting proportions such as 80% or 85% are not explicitly explained[18]. In likelihood these proportions are arbitrarily chosen from clinical experience. I believe that these levels are achievable and reasonable, but we must never forget the importance of patient involvement in the decision making in the treatment of chronic conditions[282,283].

5.12 WHERE ARE RESOURCES MOST WELL USED IN ATRIAL FIBRILLATION MANAGEMENT?

In the included primary care centers in Region Stockholm, the use of anticoagulants in patients with atrial fibrillation was 82% in 2016-17. The treatment proportion is currently ≥75% in all age groups (when studying men with $CHA_2DS_2VASc \geq 2$ and women with $CHA_2DS_2VASc \geq 3$). This means that research interventions with the goal of improving medication use further, in likelihood would be resource consuming relative to the small expected increases in medication use. The recently published ESC atrial fibrillation guidelines emphasize the importance of a holistic approach to the management of atrial fibrillation, in which strategies to promote medication adherence is only one of several components[21]. In our setting, with high use of anticoagulants, the approach of shifting focus from medication use improvement to managing cardiovascular comorbidity, lifestyle factors, psychosocial factors, and patient self-management seems reasonable. However, in settings where use of anticoagulants is still low, of course more resources are warranted towards purely improving medication use. Worthy of note among planned interventional trials is "STEER-AF"[284]. Patients with atrial fibrillation will be included from approximately 70 centers in six European countries. The centers will be randomized to a comprehensive educational intervention targeting healthcare professionals, or to no intervention. Among the outcomes being studied are guideline adherence among healthcare professionals; guideline

adherence for rhythm control and stroke prevention; proportion of patients with appropriate anticoagulant use; and in the long term also clinical events.

6 MAIN STRENGHTS AND LIMITATIONS

6.1 STRENGHTS

All our studies have used registries/databases with high validity, thus ensuring a *high quality of data*. The registries/databases have allowed for research on *unselected, sizeable cohorts* in a region of approximately 2 million inhabitants with a *uniform healthcare system*. *Linkage of data* between registries in Sweden is advantageous and enables the combining and use of different kinds of data. *Including approximately 200 primary care* centers in an intervention is another strength specific to study III and IV. The availability of *data from both national registries and primary care* in studies II-IV enables analyses that are currently not possible on the national level.

6.2 LIMITATIONS

Many of the limitations of the studies in this thesis have already been mentioned in the methodological considerations section (section 3) and this section should be examined by the reader for a more complete picture.

6.2.1 Generalizability

Our studies were conducted in Region Stockholm with the advantages elaborated on in the "strengths" section. While there are advantages of studying a defined region, it must be recognized that our results may not be generalizable to other regions abroad, or in Sweden. Medication use and diagnosing recording patterns in ischemic stroke/TIA/atrial fibrillation likely have regional variations within and outside Sweden. Also, healthcare is organized differently in different areas of Sweden and internationally. For example, the fact that our intervention in studies III and IV was neutral is likely generalizable to other urban, high-income country settings with high baseline medication use. It cannot be excluded that similar interventions would have an effect on medication use in other settings. Diagnosis recording may be influenced by regional financial incentives and healthcare organization, thus limiting the generalizability of the results in study II.

6.2.2 Not all patients in Region Stockholm were included in the unpublished analyses

The additional unpublished analyses in this thesis have been performed using the same inclusion and exclusion criteria as in the original publications. For study III and IV, this meant excluding patients that are not listed at any primary care center, patients living in nursing homes; deceased patients; patients <18 years of age, and patients in the excluded primary care centers. If I had only excluded deceased patients or patients not living in Region Stockholm, there would have been 15 550 patients (instead of 12 766) in the analysis in study III, and 37 401 patients with CHA_2DS_2VASc score ≥2 (instead of 31 477) in study IV. Thus, the use of preventive medication in all patients in Region Stockholm may differ somewhat to the unpublished analyses of study III and IV presented in this thesis.

6.2.3 Definition of medication use

6.2.3.1 Medication dispensation does not equal actual intake of medicine.

While medication use in all the studies in this thesis has been defined as medication dispensations, it should be appreciated that simply picking up a medication in the pharmacy does not equal actual intake of medication. However, dispensation is likely the best option when conducting large studies on medication use.

6.2.3.2 Defining medication use as two dispensations

Defining medication use as two medication dispensations is somewhat arbitrary. For this reason the sensitivity analyses that we have carried out are important, when medication use is defined as different numbers of dispensation. Possibly, three or even four dispensations could have been used as the baseline definition of medication use during an 18-month period. With three or four dispensations as a starting point, sensitivity analysis of more and less dispensations could have been performed. However, choosing to have another baseline for number of dispensations defining on-treatment would have been just as random as defining treatment as two dispensations. Choosing multiple dispensations may be better than just a single dispensation when defining treatment, since one dispensation could mean that a patient has quit straight away after starting. Multiple dispensations implies an intent to continue treatment on the patient's part.

6.2.4 Where does the problem lie – prescriber or patient? No prescription data

The studies in this thesis have all used medication dispensation as an end-point. Our study design cannot establish how much of non-medication use is related to patient factors – i.e. not picking up existing prescriptions, taking medication irregularly – and how much is related to physician factors – i.e. not prescribing, failing to motivate patients, not addressing side-effects adequately etc. It is possible to know what medications patients are prescribed through RiksStroke, but information is only available at the index event. Being able to use prescription data from primary care would be very valuable in future studies of long term, chronic medication use. However, this type of prescription data is not currently available in Sweden.

6.2.5 Residual confounding in database research

We have attempted to use the available registries as thoroughly as possible with regards to obtaining, and adjusting for, confounding. However, in research, and registry research in particular, there will often be residual confounding – i.e. the existence of confounders which have not been adjusted for.

When studying the association of an exposure and an outcome it is important to appreciate that the association may be caused by a confounder. A confounder is a factor which is associated with both the exposure and the outcome variable. There are several ways to handle

confounding. One way is to adjust for confounding factors in the analysis phase of a study. In order to adjust for a confounder, we must have data on that confounder. In registry research, we are constrained by the fact that we only have the data which the registry provides us with. Therefore, there may be numerous confounders which we cannot adjust for, simply because we do not have data on them. The NPR and VAL do not have data on lifestyle factors such as smoking, physical activity, alcohol use, occupation etc. In study I we could adjust for socioeconomic factors, which were not available in studies II-IV. In study III-IV we had data on comorbidity and primary care center characteristics which were not available in the data set in study I. It should be noted that we could have acquired, and adjusted for, more data on comorbidities in study I. Data was available in VAL, but was not included in our data set. So sometimes the variable of interest does not exist in the registry of interest (e.g. smoking), and sometimes it does exist but has not been extracted and used in the data set.

6.2.6 Multiple analyses and type I errors

When working with a large data sets and carrying out numerous analyses, it should be appreciated that the risk of making a type I error increases. A type I error is a situation where the null hypothesis is actually true, but is falsely rejected, i.e. the findings are reported as significant when they are not. This has likely not been a problem in the analyses in the studies included in this thesis.

6.2.7 Insufficient analysis of the intervention in study III and IV

Our audit & feedback intervention in primary care showed neutral results. We do not know if the cause of these neutral results was lack of dissemination/use of the intervention, or the content in itself. We did send out a questionnaire to all primary care center directors with questions about the intervention, but this was done in the autumn of 2018. The response frequency was low (12%). Some centers had changed directors since the intervention and had not heard of it. A questionnaire in late 2016 would have been more appropriate. This would likely have resulted in a higher response frequency. Furthermore, it would have been interesting to perform more in depth, qualitative, interviews with a sample of the primary care center directors. This may have allowed for a better understanding of their reasons for using, or not using, the intervention.

7 CONCLUSIONS

- Use of recommended preventive medications in Region Stockholm has increased over time in both patients with prior ischemic stroke/TIA and patients with atrial fibrillation.
- Women in Region Stockholm use less statins than men after ischemic stroke/TIA. The sex gap in statin use after ischemic stroke/TIA has persisted over time and it is important that measures are taken to improve treatment in women.
- High income was associated with being dispensed more statins, anticoagulants, and antiplatelets 9-12 months after ischemic stroke/TIA in Region Stockholm.
- Having a diagnosis recorded in primary care was associated with using more secondary preventive medication after ischemic stroke, hemorrhagic stroke, TIA, and acute coronary syndrome in Region Stockholm.
- An audit & feedback intervention did not improve the use of preventive stroke medications in primary care in Region Stockholm.
- Diagnosis recording of TIA and atrial fibrillation was slightly better in intervention centers than control centers, after (but not before) an audit & feedback intervention in Region Stockholm. However, absolute differences between groups were small.
- An audit & feedback intervention did not have any effect on diagnosis recording in patients with previous ischemic stroke.

8 FUTURE PERSPECTIVES

8.1 INCREASING STATIN USE IN WOMEN

Statins appear to be the preventive medication class which requires most attention, relative to the other classes where use is better. Improving statin use in women would achieve both increased statin use in the entire population, but would also target sex inequalities. Thus, a study with the intention of increasing the use of statins in women after ischemic stroke/TIA should be a top priority for future research. It could be called the Bringing Equality to Statin Treatment study or the BEST-study. This study has not yet been planned so the design of an intervention has not been defined. Speculatively, the intervention would likely be carried out in all of Region Stockholm, with another comparable Swedish region as control. Potential contents of an intervention to increase statin use have been previously discussed in this thesis. Additionally, hospitals and primary care centers could be provided with sex specific audit & feedback statin prescription and dispensation data on their stroke/TIA patients.

8.2 A STUDY WITH BOTH PRESCRIPTION AND DISPENSATION DATA

It would be interesting to conduct a study on the long term medication use in patients with ischemic stroke/TIA using RiksStroke data on prescription, and dispensation data. A time period of five years after an initial event could be used. In this study we could document prescription and primary non-adherence as well as long term persistence and adherence. We could also use "dispensations in a time period" to define treatment after five years and see how this relates to adherence and persistence. Interesting questions to answer would be for example – do patients who have been defined as non-persistent in previous, shorter, studies actually start treatment again?

8.3 BETTER UNDERSTANDING OF DIAGNOSIS RECORDING

The underlying processes/mechanisms which determine if a primary care physician chooses to record or not record a diagnosis are poorly understood. Qualitative studies with primary care physicians are needed, as well as comparisons of diagnosis recording habits across different healthcare regions in Sweden, with different reimbursement systems for recording.

8.4 REPEATING STUDIES ON SOCIOECONOMY AND MEDICATION USE

As has been mentioned previously in this thesis, the associations between socioeconomic factors and medication use may have changed over time. Thus, repeating previous studies may be of value.

9 SAMMANFATTNING PÅ SVENSKA

Bakgrund: Mediciner kan förebygga insjuknande i stroke men används inte alltid i tillräcklig utsträckning av patienter. Det övergripande syftet med denna avhandling var att studera medicinanvändning hos patienter med tidigare ischemisk stroke eller transitorisk ischemisk attack (TIA), och hos alla patienter med förmaksflimmer. Socioekonomiska- och demografiska faktorer som kön, inkomst och utbildning har associerats med skillnader i medicinanvändning efter stroke. Om man kan få bättre insikt kring dessa associationer kan det förbättra förståelsen av varför medicinanvändningen hos patienter är otillräcklig. Patienter med tidigare stroke följs långsiktigt inom primärvården i Sverige. Därför är det rimligt att interventioner med syfte att förbättra medicinanvändning fokuserar på vårdcentraler. Efter varje patientbesök hos läkare på vårdcentral behöver läkaren registrera en diagnos för besöket, som förs in i den elektroniska patientjournalen. Denna diagnosregistrering har föreslagits som en möjlig kvalitetsindikator för god vård inom primärvården. Dock är diagnosregistrering fortfarande otillräckligt studerat för att veta om det skulle vara användbart som en sådan indikator. Associationen mellan läkemedelsanvändning och diagnosregistrering har inte studerats. ”Audit & feedback” (ungefär ”Granska & återkoppla”) är en vanlig och välstuderad metod för att åstadkomma beteendeförändringar hos sjukvårdspersonal. Om en intervention gentemot primärvårdsläkare skulle lyckas öka läkarnas förskrivning av förebyggande läkemedel och motiverande av patienter med stroke/förmaksflimmer att ta dessa, skulle medicinanvändningen potentiellt kunna öka.

Metoder: Alla studier i denna avhandling är registerbaserade och har inkluderat patienter ≥18 års ålder i Region Stockholm. Utfallsmåttet i alla studier har varit medicinanvändning. Från det svenska Läkemedelsregistret har vi kunnat använda uthämtade läkemedel på apotek som ett mått på medicinanvändning. I studie I länkades data från VAL (se nedan), Läkemedelsregistret och Statistiska Centralbyrån. I studier II-IV användes databasen för uppföljning och analys av sjukvårdskonsumtion och produktion i Region Stockholm – VAL databasen. Data i VAL är identisk med data i Patientregistret och sedan 2010 också Läkemedelsregistret. I studie I undersökte vi associationen mellan sociodemografiska faktorer och medicinanvändning 9-12 månader efter ischemisk stroke/TIA. I studie II undersökte vi associationen mellan diagnosregistrering i primärvård och medicinanvändning hos patienter med tidigare stroke/TIA och akut koronart syndrom. Studie III och IV testade om en ”audit & feedback” intervention riktad till primärvårdsläkare kunde förbättra medicinanvändning hos patienter med tidigare ischemisk stroke/TIA (III) eller förmaksflimmer (IV).

Resultat/slutsatser: Strokeförebyggande medicinanvändning av alla rekommenderade läkemedelsklasser har ökat över tid hos patienter med tidigare ischemisk stroke/TIA och hos patienter med förmaksflimmer. Statiner är den läkemedelsklass som används minst efter ischemisk stroke/TIA, och kvinnor använder mindre statiner i alla åldersklasser. Framtida interventioner bör sträva ha som mål att jämna ut könsskillnaderna i statinanvändning. Högre inkomst var associerat med ökad användning av statiner, antikoagulantia och

trombocythämmare 9-12 månader efter ischemisk stroke/TIA. Diagnosregistrering var associerat med ökad läkemedelsanvändning hos patienter med stroke/TIA, akut koronart syndrom och förmaksflimmer. En ”audit & feedback”-intervention lyckades inte förbättra läkemedelsanvändningen hos primärvårdspatienter med tidigare ischemisk stroke/TIA eller förmaksflimmer.

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